THE CLINICAL DIAGNOSIS OF INTERNAL DISEASES

THE BLOOD, DIGESTIVE SYSTEM AND UROLOGY

**

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Part VII

Diagnosis of Diseases of the Blood and of the Blood-Building Organs

Section I

METHODS OF EXAMINATION

A. General Introduction

The blood is the medium of communication among the different organs and cells of the body. It is the nutrient fluid of the organism and is of great metabolic significance. It permits of the exchange of gases in the lungs and tissues, takes the substances that act as foods and as chemical and physical stimuli to the cells that are to receive them, and, in turn, carries off the excretory products of the cells. Through it, the products of the various internal secretions, the hormones like adrenalin and secretin, are carried about the body; thus the blood and the nervous system together maintain the intimate relationships that exist among all of the single parts of the body. The organs of excretion and disintoxication remove from the blood various waste matters and harmful substances dissolved in it. Its close relations with all the body cells explain why an abnormality of the blood can ultimately affect the whole organism, and, also, why any local disease of an organ can in turn lead to a disorder of the blood. Indeed, every disease of an organ is at the same time a disease of the blood.

In recent years, very important advances have been made by clinicians in the study of the blood. An examination of its formed elements (*morphological-biological methods*), a study of its constituents by physical and chemical methods (*physical-chemical methods*), and an investigation of its contents for vegetable and animal parasites, for ferments, and for antibodies (*bacteriological-parasitological-serological methods*) often yield valuable help in diagnosis.

Morphological methods have thus far been, perhaps, most serviceable in clinical diagnosis, though recently parasitological and serological

methods have begun to be extensively cultivated, and the time will doubtless come when the many physical and chemical methods now being worked out by special investigators will become of value to the medical practitioner.

The morphology of the red corpuscles, and more particularly of the white corpuscles, has been most exhaustively studied in health and in disease. Studies of the blood platelets have, too, begun to be significant clinically. We now possess a mass of facts concerning leukocytosis, leukopenias, anemias, and leukemias, the importance of which will scarcely be underestimated, even by those whose tendency is to depreciate the contributions of laboratory workers to the clinical sciences.

Physical and chemical methods of studying the blood are, on the whole, more time-robbing, and more difficult, than the morphological methods. Thus far, too, the "yield" in practical results for diagnosis and therapy has been relatively small. But the outlook for these methods is becoming more promising as investigators, more and more, devote their energies to them. The researches bearing upon the total quantity of the blood, on hemolysis, on coagulation and thrombosis, and on the fermentative activities of the blood (especially Abderhalden's reaction) seem to be full of promise.

Studies of the blood made by bacteriological, parasitological, and serological methods, have already yielded results of enormous value not only from the theoretical, but also from the practical side. The newer doctrines of infection, immunity, and anaphylaxis have been built up, largely, by means of examinations of the blood. We now make a positive diagnosis of typhoid fever within a day or two after the patient has taken to his bed, by means of a blood culture. One of the first things we now do in the routine examination of a patient entering a hospital for diagnostic study, whether he enter the private or the public ward, is to test the blood by means of the Wassermann reaction, so easily and quickly is it possible to make tolerably sure of the presence or absence of a luetic infection. Malaria has lost its mystery with the advent of systematic blood examinations; no longer does the trained clinician deluge his patient with quinin for an intermittent, or a remittent, fever, when the blood, on repeated examination, is found to be free of malarial parasites and malarial pigment.

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1. Brief Review of the Physical and Chemical Properties of the Blood

The blood consists of a fluid portion (plasma), and of certain formed elements (red and white blood-corpuscles and blood platelets) suspended in the fluid.

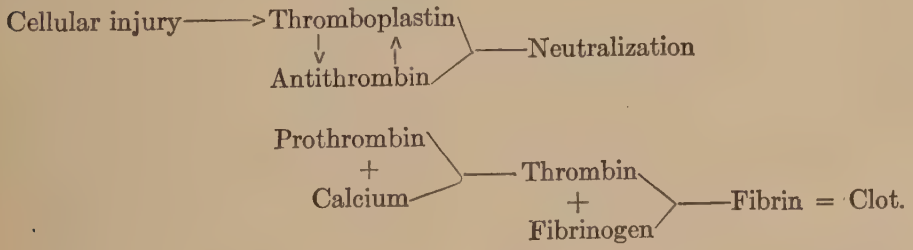
(*a*) *Coagulation of the Blood*

If a portion of the blood be drawn and allowed to stand, it will soon coagulate, owing to the fact that the fibrinogen of the plasma is changed into fibrin; the resulting clot, or coagulum, contains in its meshes of fibrin, the cellular elements, and the blood platelets. The fluid blood-plasma, having been deprived of its fibrinogen, leaves a clear, straw-colored fluid (serum) behind. If the blood be beaten during coagulation, the fibrin can be removed, separate from the rest of the blood, in which case the defibrinated blood contains serum, red and white blood-corpuscles, and blood platelets.

The usual account given of the coagulation of the blood attributes this phenomenon to the action of a ferment (thrombin, or thrombase), which converts the soluble fibrinogen into insoluble fibrin. The ferment (thrombin), in turn, is described as absent from the circulating blood, but, when blood comes in contact with foreign substances, it arises from a substance in the plasma known as thrombogen, or prothrombin (possibly derived from the blood platelets), through activation by a thrombokinase (a substance said to be present especially in the blood cells and in the cells of the walls of blood vessels).

In addition to the ferment, thrombin, ionized lime salts must be present, if fibrinogen is to be converted into fibrin; if these salts be precipitated by a small quantity of potassium oxalate or sodium citrate (0.1-0.5 per cent), coagulation is prevented. Coagulation can also be hindered by the addition of solutions of pepton, or of leech extract (hirudin, 1 mgr. to 4 ccm. blood), and it can be delayed by cooling the blood.

Recent studies by W. H. Howell have tended to establish a simpler theory of blood coagulation than that described above. Howell assumes that all the elements necessary for coagulation are present in the circulating blood, namely, prothrombin, fibrinogen and calcium, and that there is normally sufficient antithrombin present to neutralize and inactivate the prothrombin. The balance between these two is extremely delicate, though capable, normally, of rapid adjustment. Cellular injury releases a substance, known as thromboplastin, which binds the antithrombin and permits the other three components to act in the manner shown in the diagram below.



It will be seen that Howell's view differs from the view previously described (1) in the assumption that thrombin consists simply of calcium

and prothrombin (free to act), and that it does not have to be activated by a thrombokinase, (2) in stating that thrombin in the presence of fibrinogen is inhibited from acting by antithrombin, and that as soon as antithrombin is neutralized by thromboplastin, coagulation occurs. Upholders of the earlier view may perhaps reconcile their theory with Howell's by (1) granting that prothrombin and calcium are normally present in plasma, and (2) accepting Howell's "neutralization of antithrombin with thromboplastin" as a paraphrase of their "activation by thrombokinase."

This view of Howell's satisfies the known facts of coagulation better than any other theory thus far advanced, and it is full of promise of applications in clinical work, both diagnostic and therapeutic. All practical workers in hematology will do well to familiarize themselves with Howell's views and with the technic of his methods of work.

The methods for determining the "coagulation time" and the "bleeding time" in human beings will be described further on.

Clinicians have tried to find out methods for shortening the coagulation time (administration of calcium lactate, gelatin injections, NaCl injections, serum injections, coagulin of Clowes, etc.), for it is often desirable, clinically, to shorten the coagulation time in cases (1) of severe internal hemorrhage, (2) of hemorrhagic diathesis (hemophilia, scurvy, icterus, etc.), and (3) of aneurism. Surgeons, particularly, in cases of jaundice and in other cases with hemorrhagic tendency desire to increase the coagulative power of the blood before operation. The newer studies on the fibrinogen content, and on the prothrombin and the antithrombin content of the blood promise to enlighten us regarding the nature of such cases (Whipple and Moss).

In other clinical cases, it may be desirable to inhibit coagulation; *i. e.*, to retard the coagulation time. In animals, it is easy to do this with hirudin. For human cases, we do not know how to act.

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(b) *Total Quantity of Blood; Volume-Percentages of Corpuscles and Plasma; Volume-Index (Capps); Water-Content*

The *total quantity* of blood (by weight) in the adult body, determined by the carbon-monoxid method of Haldane, amounts to approximately one-twentieth of the body weight, or about 3½ kilos; the older methods of determination (by infusion, etc.), indicated an amount equal to about 1/13 of the body weight, which was far too large. In the anemias, the amount may be only ½ or ⅔ the normal.

Physiological and pathological changes in the total volume of the blood, and of the volume percentages of the corpuscles and the plasma, must always be remembered, since they are of importance in judging the results of various blood examinations. The *volume of the red cells* depends chiefly upon their number, but also, partly upon the osmotic pressure. The methods of determining the volume of the corpuscles (sedimentation of oxalated blood; centrifugalization in the hematokrit; determination of electrical conductivity) are notoriously unreliable, and are of but little value for routine clinical examinations. But the careful work of Capps has shown, that, critically used, some important information can be derived from them by research workers in hematology. About 45-50 per cent of the volume of the normal blood is occupied by the corpuscles. If 50 per cent be taken as the normal value and made = 1, we can express pathological volumes as *percentages of the normal volume* 1. If after determining the percentage of the normal volume present we make an ordinary red blood-corpuscle count this gives us the percentage of the normal count (5 million) present in the case under examination. From these two percentage-values, Capps determines the average volume of the corpuscles, or what he designates as the *volume-index:*

$$\frac{\text{Percentage of the normal volume}}{\text{Percentage of the normal count}} = \text{average volume} = \text{volume-index.}$$

Normally, the volume-index is, of course, 1; in pernicious anemia, Capps found it to be greater than 1, in other anemias, less than 1. This volume-index (Capps), or volume-quotient, or volume-value (Sahli), runs parallel to the color-index, to be described further on.

In certain conditions in which the red corpuscles are greatly increased in number (polycythemias), the percentage volume of the corpuscles may be greatly increased.

Certain terms are employed to denote alterations in the volume of the blood and of the blood percentages, chief of which are the following:

Oligemia.—By this is meant a *reduction of the total volume of blood,* involving both the total liquid and the total mass of cellular elements, though the blood in a unit of volume, say a cubic millimeter, may show no marked alterations. Such an oligemia occurs (1) in the severe hemolytic anemias, (2) in states of inanition (tuberculosis, carcinoma), and (3) probably in the so-called pseudoanemias, in which the persons look pale, and yet have a normal red-corpuscle count and a normal percentage of hemoglobin in the blood examined. Some of the polar anemias, and some of the tropical anemias—not all of either—belong here.

Plethora.—In this condition there is an *increased volume of blood*—permanent or transitory—due to an excess of either the serous, or the cellular, elements, or both. The specific gravity of the blood is usually increased. Such a plethora is present in cases of polycythemia (in both primary and secondary forms); there may be double the normal volume of blood, or even more. In chlorosis, there is a very large increase in the total quantity of blood (Lorrain Smith, Oerum).

Hydremia.—By this is meant a disproportionate amount of water in the blood as regards the solids; it may result from either an increase in the water of the blood, or from a decrease of the proteins (*hypalbuminosis*), and is associated with a reduction in the specific gravity. Sometimes a hydremia, as in some of the nephropathies, is associated with plethora.

Recently, a good deal of attention has been paid to the *water-content* of the blood in the various hydremias and anhydremias. Normally, the water-content, both of the blood serum and of the blood corpuscles, is tolerably constant. Temporary changes are, however, seen. Thus, the blood undergoes temporary dilution after abundant water drinking, but the normal condition is quickly restored by diuresis, or by an increase of the water in the tissues. On the other hand, the blood may become temporarily concentrated after sweating, or on a small fluid intake; here again the normal water-content tends to be maintained by corresponding drying of the tissues. The relation of changes in the blood pressure, and in vasomotor conditions generally, to the water-content, has also been studied. Thus, after adrenalin injections, the blood pressure rises and the water-content of the blood diminishes, within a few minutes, by more than 15 per cent (Hess and Erb). The changes in water-content after hard mus-

cular work may depend, partly upon blood-pressure changes, partly on sweating, and partly on changes in the content of the tissues in water. Much work needs to be done in the study of the effects of hydrotherapy (hot and cold) on the water-content of the blood. A beginning has already been made (Grawitz, Loewy).

Under pathological conditions, the same tendency of the blood to maintain its normal water-content is seen, but greater variations are met with. Thus, the water-content may be much lessened when the water-intake is interfered with (cancer of the esophagus, pyloric stenosis), or when large amounts of water are lost owing to diarrhea (Asiatic cholera, cholera nostras, severe purgation). Loss of water through the kidney less often causes diminished water-content of the blood. In diabetes mellitus, and even in diabetes insipidus, the water-content may not deviate far from the normal values.

The water-content may be increased in pathological conditions, either from a diminution in the proteins of the blood plasma, or from an increase of the water in the blood. Sometimes, both conditions occur simultaneously.

In the hydremias associated with inanition (malignant neoplasms, tuberculosis, severe anemias) there is a diminution of the proteins of the blood, and though the total water may be diminished, the relative water-content is, as a rule, markedly increased. There are, however, exceptions, the protein-content and water-content diminishing equally—a true oligemia.

After severe hemorrhages, the body tends to restore the total quantity of blood by the absorption of water from the tissues; but it may be some time before there is a complete qualitative restoration through regeneration of the proteins.

In chlorosis, the total quantity of blood is often markedly increased (plethora), but, strange to say, examination of the water-content shows, as a rule, nearly normal values. This points to an increase in the proteins of the blood in chlorosis. In pernicious anemia, the water-content is often relatively increased, but it may sometimes be normal, despite a marked lowering of the specific gravity of the total blood, owing to the diminution in red corpuscles.

From the clinical standpoint, the two most interesting forms of hydremia are (1) the *hydremia occurring in the nephropathies,* and (2) the *hydremia occurring in the cardiopathies with failing compensation.* In acute nephritis with edema, there is often a marked hydremia, the specific gravity of the blood falling as low as 1.018. The hydremia and the edema do not, however, go parallel to one another. In the chronic edematous nephropathies, hydremia is common, but in the chronic nephropathies without edema (*e. g.*, contracted kidney), hydremia as a rule does not occur. In the late stages of contracted kidney, when myocardial insuffi-

ciency sets in and edema appears, a hydremia may be found, but this is due to the circulatory, rather than to the renal, condition.

The older physicians thought that the hydremia in the nephropathies might be due to the loss of albumin through the urine, but this is not the case. It depends, in all probability, upon several factors (water retention, vascular changes, retention of electrolytes, changes in absorptive power of colloids).

In the cardiopathies, hydremia does not occur as long as there is compensation, but when myocardial insufficiency appears, hydremia develops, probably due to water retention. If the myocardial insufficiency persist long, the hydremia diminishes, owing chiefly to an increase in the red corpuscles of the blood, but partly to an increased excretion of water through the lungs (dyspnea).

Anhydremia.—This condition is characterized by a decrease in the liquid constituents of the blood, with a resultant concentration of the proteins (*hyperalbuminosis*), and of the formed elements.

(*c*) *Color of the Blood; Hemoglobin; Blood Gases*

The color of arterial blood is normally bright red, owing to the large amount of oxyhemoglobin in it; the venous blood, less rich in this substance, is darker, more bluish red. The amount of hemoglobin present, in health, in a normal adult is 13 or 14 grams in 100 c.c., being a little less in women than in men. As a general standard for the normal adult, 13.77 g. in 100 c.c. has been adopted, but the amount varies markedly in normal adults. (See Methods of Examination of the Hemoglobin-content of the Blood.) The amount varies normally also with the age of the person, and can be charted out in a definite curve. The common figures are those of Leichtenstern, given in the table below.

Amounts of Hemoglobin at Different Ages.—

Age.	Grams of Hemoglobin per 100 c.c. of Blood.
1 to 4 days	19.329 to 21.16
8 to 14 "	16.124 to 17.869
8 to 20 weeks	12.928 to 15.362
6 mo.—5th year	10.971 to 11.373
5 to 15 years	11.151 to 11.796
15 to 25 "	13.034 to 13.870
25 to 45 "	14.727 to 15.013
45 to 60 "	12.484 to 13.150
Over 60 "	14.79

The combining power of reduced hemoglobin for O_2 and for CO is well known; 1 gram of the coloring matter will combine with 1.34 c.c. O_2, or with the same amount of CO at 0° C. and 760 mm. barometric pres-

sure. The idea, formerly held, that several varieties of hemoglobin exist, each having a different combining power, has been given up.

The Gases of the Blood.—The arterial blood in animals contains about 21.6 per cent by volume of oxygen, loosely combined with hemoglobin; studies in man have seldom been made on the arterial blood. The venous blood contains only 14.8 per cent of O_2 by volume, though the percentage varies greatly.

The arterial blood contains about 40.3 per cent of CO_2 by volume (one-third of it united to the red corpuscles, the rest in the plasma); the venous blood, 46 per cent to 48 per cent by volume. Both venous and arterial blood contain 1.8 per cent by volume of nitrogen, as well as traces of argon.

One must never judge of the amount of hemoglobin merely by the pallor of the mucous membranes. It takes only a little experience to teach one how far astray such a guess may lead. Many people look very pale and still have over 90 per cent of hemoglobin (pseudoanemia).

There is a good deal of evidence that the *tension* of the gases in the blood may be of more importance than the actual *quantity,* as far as their biological significance is concerned. The tension is, to a certain extent, independent of the quantity. Bohr has shown that an abundance of CO_2 increases the tension of the oxygen present, while the CO_2 tension itself is affected by changes in the titratable alkalinity. The greater the degree of acidosis, for example, the higher the CO_2 tension, even when the quantity of CO_2 remains constant (dyspnea from exertion, coma diabeticum).

The *cause of dyspnea* probably lies in alterations in the blood gases. The dyspnea of anemic patients is due to the diminished oxygen-content of the blood, which goes parallel with the diminution of hemoglobin. The dyspnea here accelerates the circulation, and so is, to a certain extent, a purposeful phenomenon.

The dyspnea occurring at high altitudes (mountain climbing, aeroplane) is due to stimulation of the respiratory center from lack of oxygen in the arterial blood. The dyspnea of open pneumothorax has the same cause.

In cardiac dyspnea, the blood contains an excess of CO_2; in cyanosis, the CO_2-content may rise to 60-70 per cent (Morawitz). The tension of the CO_2 in such cases has only recently been studied (Porges); it seems likely, from the newer studies, that cardiac dyspnea is also, in reality, due to lack of oxygen. Thus far, only venous blood has been studied in such cases; it is desirable that gas analyses of the arterial blood in experimental animals should be undertaken to throw light upon this point.

In asphyxia, the oxygen-content of the blood falls in a few minutes to a very low level, the CO_2 content rising rapidly (Setschenow).

In carbon-monoxid poisoning the oxygen is prevented from uniting with the hemoglobin, and the oxygen-content of the blood falls; at the same

time the CO_2 content falls, probably owing to decrease of the titratable alkalescence (Loewy).

In prussic-acid poisoning, the venous blood contains an excess of oxygen, and is poor in CO_2, owing to the loss of power of the tissues to take up oxygen from the blood (Geppert); this accounts for the bright red color of the venous blood in such cases.

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(*d*) *Reaction and Reactivity of the Blood; Its "Acid-Capacity"*

The potential reaction of the blood, tested by titrimetric methods, is alkaline, though the alkalescence is somewhat variable according to the indicator used.

This alkalescence is really an expression of the acid-combining power of the blood; the blood also possesses alkali-combining power, but to a less degree. In terms of free hydroxyl (OH) ions and of free hydrogen (H) ions, which physical chemistry employs as the gauge of alkalinity and of acidity, *the "actual" reaction* of normal blood is almost neutral. In health, the values of free H and OH ions obtained by the "gas-chain" method of Michaelis are very constant ($0.26–0.30 \times 10^{7}$). Even in disease, including diabetic coma, the values remain within the limits $0.1–1 \times 10^{7}$. According to F. W. Peabody (1914), the free H-ion content is increased, the OH-ion content diminished, in the blood in uremia; though the studies of Michaelis and Davidoff, of Masel, and of F. M. McPhedran, indicate normal findings in uremia.

The *"potential" alkalescence*, revealed by titrimetric methods, depends, with any given indicator, upon (1) a diffusible fraction (due to Na_2HPO_4, $NaHCO_3$, and Na_2CO_3), and (2) a non-diffusible fraction (due to proteins, in the cells and in the plasma). Since the blood is "actually" neutral, and what we measure, on titration, is in reality the amount of acid we may add without raising the concentration of the hydrogen ions above a certain low limiting value (variable with the indicator), it is

better to use the term "reactivity" of the blood (Moore and Wilson) for the property it possesses of combining with acids, though it be neutral, without changing its H-ion content.

The titratable alkalescence of the blood is diminished in fever (von Jaksch, Kraus), though the alteration is not constant. It has been thought that resistance to infection stands in relation to the alkalinity of the blood, but this seems improbable. The remarkable lessening of the alkalescence, or of the acid-capacity, of the blood in cholera (Cantani, Sellards) has yet to be explained, especially as concentration of the blood usually increases alkalescence. The diminished acid-capacity in uremia has recently attracted much attention (von Jaksch, Sellards, Brandenburg). Uremia appears to be one of the few pathological conditions in which the "alkali tension" (diffusible alkali) is diminished. The diminished capacity for binding acid in some cases of chronic nephropathy with uremia, as measured by Sellards, in the clinic in which I work, is remarkable.

(*e*) *The Specific Gravity of the Blood*

The *specific gravity of the blood* varies, in health, between 1.055 and 1.062 in men, and between 1.050 and 1.056 in women, depending chiefly on its hemoglobin content, the age of the person, and the temperature at which the estimation is made. In pathological conditions, the blood may become very concentrated (sp. gr. 1.080), or very dilute (sp. gr. 1.030).

The *specific gravity of the blood serum* varies normally between 1.029 and 1.032, depending chiefly upon its protein-content. When the specific gravity is low, a condition of hydremia exists. But the specific gravity may be normal, even when the blood is impoverished in protein, owing to an increase in dissolved salts (*e. g.*, in uremia). For clinical purposes, a knowledge of the specific gravity of the blood is, as yet, of little or no value.

(*f*) *Molecular and Ionic Concentration of the Blood; Osmotic Pressure; Electrical Conductivity*

The *freezing point* of the blood, determined by cryoscopy, varies in health within very narrow limits, being extraordinarily constant, usually lying close to – 0.56°C. Since proteins have almost no osmotic value, the exact position of the freezing point of the blood (δ) depends upon the content of the blood serum in crystalloid substances, especially in salts. The amount of sodium chlorid in the blood serum is normally 0.7 per cent; the amount of nitrogen, other than that in coagulable protein, that is to say, the "Rest"-nitrogen, amounts in health from 20 to 35 mg. of N in 100 c.c. of blood. The amount of CO_2 in the blood influences the freezing point; thus in the cyanosis of emphysema, or of myocardial insufficiency, δ may be low, though if the CO_2 be driven off, it may become normal. It

was hoped that the determination of δ would be a help in the diagnosis of uremia; thus far it is of no practical clinical value.

The determination of the *electrical conductivity* of the blood has as yet yielded no results of clinical importance. As Ralph W. Webster emphasizes, the fact that the electrical conductivity of the blood serum is not much increased in the cases of severe advanced renal disease, even when the freezing point is lowered, makes it probable that the retention of chlorids in renal disease does not mean that they are retained in the blood; they probably go out into the tissues, the lowering of the freezing point that is observed being due to non-dissociable molecules (probably organic, rather than inorganic, constituents).

(g) *Permeability of the Red Blood-Corpuscles; Osmotic, Thermal, Mechanical, and Hemolytic Resistance*

The red corpuscles act like semi-permeable membranes. They allow water to pass in and out, with change in their volume, but they are not permeable to salts. An exception must, in this far, be made that exact studies have shown that certain anions (Cl', CO_3'', NO_3', SO_4'') can pass in, provided other ions pass out in compensation; but kations (K, Na, Ca, etc.) do not pass through at all. The quantity of CO_3''-ions in the red corpuscles is of marked influence on the *permeability*. From solutions, equimolecular in concentration with the content of the red corpuscles, these corpuscles have no power to draw water; in other words, such solutions are *isotonic* with the corpuscles—they have identical *osmotic pressures*. An example of such an isotonic solution is an 0.9-per-cent solution of NaCl. In an NaCl solution stronger than 0.9-per-cent, water is drawn out of the corpuscles, and they shrink; such a salt solution is *hypertonic*. On the other hand, in an NaCl solution weaker than 0.9-per-cent, the water is drawn into the paraplasma of the red corpuscles, and they swell up; such a salt solution is *hypo-tonic*. On marked swelling of the corpuscles, they lose their hemoglobin; the blood becomes "laked."

These reversible osmotic phenomena can proceed for a considerable distance in either direction without injury to the red corpuscles. On this principle, a method of determining the *resistance of the red corpuscles* by exposing them to a series of salt solutions of differing strengths (*q. v.*) has been worked out. The feeblest solution in which the blood is not laked at all is the *minimum resistance,* that is, the strength at which the most vulnerable red cells are not laked; for normal blood, this strength is 0.46-per-cent NaCl. The feeblest solution in which the least vulnerable red cells can still exist unlaked is known as the *maximum resistance*. The difference between the minimum resistance and the maximum resistance is called the *resistance-breadth*.

We can determine not only (1) this *osmotic resistance* of the cells, but

also (2) the *mechanical resistance* to shaking with glass pearls, (3) the *thermal resistance*, and (4) the *resistance to hemolytic poisons*, for example, saponin.

In the experimental anemias, the red cells may gradually attain to an enormous increase in resistance. Thus, in poisoning by phenylhydrazin, the resistance may be so increased that the red cells can be placed in distilled water, even after having been washed free from serum, without being laked (Morawitz and Pratt, Pratt and Itami). The increased resistance is associated with an increase in the stroma of the red cells (*pachydermia*).

In hemolytic icterus, the resistance is lower than normal; in ordinary obstructive jaundice, the resistance is plus. In pernicious anemia, there is a plus resistance. In hemoglobinuria, there is no change in the osmotic resistance, but a diminution of both the thermal and the mechanical resistance has been demonstrated (Meyer and Emmerich).

W. L. Moss has shown that human beings are subdivisible into four groups as regards sensitiveness to iso-agglutinins and isohemolysins. The technic of this determination will be given under methods of examination. It is important for the selection of a suitable donor, in cases of transfusion of blood, to be sure that the "donor" belongs to the same group as the "recipient."

(*h*) *The Viscosity of the Blood* (η)

By this is meant the internal friction of the blood, as determined by a viscosimeter (*q. v.*).

According to Poiseuille's law, fluids at equal temperature and equal pressure, passing through capillary tubes of equal caliber, vary in their rate of flow as they vary in internal friction (*i. e.*, in viscosity). The law holds good for certain pressure-differences only, and a suitable viscosimeter must provide the necessary pressure-differences (Hess).

The *viscosity* (η) depends upon a large number of factors. If an abnormal viscosity be found, it may point to any one of these several factors. Naegeli values its determination highly for purposes of quick orientation regarding a given blood-sample, since any deviation from the normal proves that we are dealing with an abnormal blood. The abnormality may not be clinically very important; thus a slight stasis will materially increase the viscosity. Naegeli has used the method to control the ways of securing blood for clinical examination; he finds that blood drawn by venepuncture is altered (by slight stasis) enough to increase the viscosity, and that the only way to secure blood of constant composition for clinical examination is to puncture the finger after the hand has been immersed in warm water for a time.

In normal adults, the viscosity of the whole blood (η) averages about 5.1, while the viscosity of the serum (η_1) is less (1.78-2.19). The difference depends chiefly upon the viscosity of the blood corpuscles, which, as a rule, make up $\frac{2}{3}$-$\frac{3}{4}$ of the viscosity of the whole blood.

Hess has shown that the normal viscosity of the blood affords the most favorable conditions for the circulation, making the pumping-work of the heart through the capillaries the least possible.

The viscosity of the whole blood is diminished in anemias and markedly increased in the polycythemias (η = 11-20). It is remarkable that, in the polycythemias with such increased viscosity, the heart does not hypertrophy. The reason probably lies either in a sinking of the minute volume, or in a dilatation of the vessels, to compensate for the increased friction.

When the CO_2 content of the blood is increased, the viscosity increases rapidly, probably owing to swelling of the red corpuscles; doubtless this gives the heart more work to do.

Recent studies indicate that the viscosity of the blood may be of importance in metabolic exchanges between the blood and the tissues. In animals, the over-living heart will work longer in a fluid of normal viscosity than in one in which the viscosity is less or greater than normal (Albanese).

C. R. Austrian (1911) has studied the viscosity of the blood, in the clinic in which I work. He found η slightly higher in men than in women. The number of red cells, the amount of hemoglobin, the quantities of the blood-gases, the amount of protein, fats and salts, all have an influence on the viscosity, but it does not vary in direct proportion to any one of them. Austrian found the average viscosity of the plasma (η_1) to be 1.8, and that $\frac{\text{Hemoglobin}}{\text{Viscosity}} = 17$ to 21. The viscosity was reduced in cases of anemia, increased in cases of diabetes, pneumonia, jaundice, and polycythemia.

O. Naegeli (1912) holds that the viscosity (η) depends on the following factors:

1. On the viscosity of the plasma or serum = η_1.
2. On the number and volume of the red corpuscles (most important factor!).
3. On the hemoglobin (almost as important as the r. b. c.).
4. In marked leukocytosis on the number and volume of the white cells.
5. On the size and the volume of the circulating cells.
6. On the nature of these cells (fullness with hemoglobin; water-content).
7. On the CO_2 of the blood.
8. On the salts of the plasma.

Naegeli maintains that η is a very desirable general control for other methods of examining the blood, and in the last edition of his textbook discusses its usefulness at considerable length. The interested reader will do well to consult this treatise, and also to study Determann's monograph.

(*i*) *Chemical Composition of the Blood*

In studying the chemistry of the blood systematically, investigators have to consider (1) the whole blood, (2) the blood plasma, (3) the blood serum, and (4) the formed elements of the blood. In the future, such analytical studies will doubtless become of considerable clinical value; at present, they can be used only

by special research workers. A few of the outstanding results of such studies will be mentioned here.

Dried Residue.—The dried residue of the whole blood (total solids) amounts to from 21-22.5 per cent by weight. The dried residue of the plasma (without the corpuscles) amounts to from 10-10.5 per cent by weight; in other words, 90 per cent of the plasma is water.

Proteins.—The *total protein content of the blood serum,* as determined by the refractometer, varies between 7.24 per cent and 9.13 per cent (Reiss). This corresponds to 1.2-1.5 per cent of the total N. In nephritis with edema, it may fall to 5.4 per cent or even to 4.8 per cent. The solids of the plasma consist chiefly of proteins (7-9 per cent). Among the proteins are the *globulins* and the *albumins.*

The *fibrinogen-content* is about 0.4 per cent; it is a typical globulin, and, from it, the fibrin is formed during coagulation. Formerly great attention was paid by the humoral pathologists to the amount of fibrin formed on coagulation of the blood. Increase in the quantity of fibrin was known as *hyperinosis,* decrease as *hypinosis.* It is known that in pneumonia, in suppurations of various sorts, in polyarthritis and in experimental pneumococcus infections, hyperinosis occurs; while in typhoid fever, smallpox, measles, malaria, in states of inanition, in severe anemias, in leukemia, and in Graves's disease, hypinosis is common.

Since, in the conditions associated with hyperinosis, it is common to find, also, a leukocytosis, some authors have assumed that fibrinogen is formed in the bone-marrow, but others believe that the liver is the most important fibrinogen-forming organ. The more recent work supports the latter view.

In the United States, the fibrinogen-content of the blood has been studied in pathological conditions, especially by Whipple. Though the amount present in man, and in experimental animals, fluctuates widely, it never, in health, falls to a dangerously low level. Goodpasture finds that, in health, it regenerates with extreme rapidity; the power of the body to reproduce it seems unlimited, an indication that it is of great importance for the body welfare. In certain intoxications (phosphorus, chloroform), the liver may be so injured that fibrinogen practically disappears from the blood (Whipple). It is no wonder, then, that ecchymoses and internal hemorrhages occur in such cases. Whipple suggests that the hemorrhagic symptoms in yellow fever, and in acute yellow atrophy of the liver, are due to lack of fibrinogen, consequent upon the accompanying hepatopathy. In cirrhosis of the liver, the fibrinogen-content of the blood may be low, a finding helpful for prognosis. The hemorrhages in hemophilia are not due to lack of fibrinogen, but to a lowering of the prothrombin-content of the blood plasma (Howell).

The relationship between the globulin and the albumin fractions in the blood plasma may be markedly disturbed at times. Normally, of 7.6 parts of total protein, 3.1 is *serum globulin* and 4.5 is *serum albumin,* the relationship of the globulin to the albumin being as 1:1.5. An attempt has been made to make use of variations in the so-called *protein quotient* $\frac{\text{albumin}}{\text{globulin}}$ as a clinical sign, but without much success. The quotient can, it is true, fall below 1, but such a change is not pathognomonic for any one disease. The results are too vague to make such examinations, as yet, clinically worth while.

The serum albumin of the blood consists of a mixture of at least two different proteins. In the blood serum are contained also *nucleoproteid, serum mucoid,* and *glutolin.*

The globulins and albumins can be removed from the blood by coagulative methods (heating); there remain, however, still some nitrogenous bodies, their content in N being known as *"the incoagulable N of the blood plasma"* or as

"rest-nitrogen." This rest-nitrogen amounts to 5-10 per cent of the total N of the blood plasma under normal conditions; in pathological states, it may be markedly changed in amount (*e. g.*, in uremia). It is the N of the *peptids, amino acids, urea, kreatin, hippuric acid, uric acid,* the *proteinic acids,* and other substances. The amount of rest-nitrogen varies considerably in normal adults. During fasting the amount is diminished; on an abundant meat diet, it rises markedly. The highest values are met with in the nephropathies; thus, in uremia, as much as 0.336 per cent rest-nitrogen has been observed (Strauss). W. A. Baetjer and R. R. Snowden have recently emphasized the desirability of following rest-nitrogen in cases in which renal functional tests are also performed.

There seems to be no direct connection between the amount of rest-nitrogen and the danger in uremia. This is in accord with the view that uremia does not depend directly on the retention of any kind of poisonous product (Sauerbruch). No marked deviations in the behavior of the rest-nitrogen from the normal have been made out in chronic parenchymatous nephritis and in contracted kidney (von Noorden).

Fats.—Among the fats, and lipoid substances, in the blood, the *total fats* have been determined by themselves, and then analyzed into their several constituents (*neutral fat, lecithin, jecorin, protagon,* etc.). Free *cholesterin* (itself an alcohol, cholesterol), the *cholesterin esters* of oleic and palmitic acid, and *oxycholesterin* can be isolated from the blood.

The *fat-content of the blood* is subject to great variations, and, especially under normal conditions, it depends upon the amount of fat taken in with the food. It is lower in the morning before breakfast in a patient on an ordinary diet than in the same patient after a prolonged fast, since, on prolonged fasting, the body has to use fat instead of sugar in its ordinary combustions, and the fat-content of the blood becomes increased, owing to the wandering of fat from the adipose tissues to the places where fat is to be burned.

Besides the temporary *lipemia* following an increased fat-intake in the food, an increased fat-content is met with in various pathological processes, especially in severe cases of diabetes mellitus, with acidosis or coma. In one case studied by B. Fischer, more than 18 per cent of fat was found.

Lipemia has also been met with in obesity, in chronic alcoholism, in phosphorus poisoning and in pregnancy. Boggs and Morris have demonstrated the presence of lipemia in toxic and in posthemorrhagic experimental anemias in the rabbit; as much as 4 per cent of fat may be present in the blood. When lipemia exists, the blood serum is usually turbid and milky-looking; in severe grades, the whole blood may look like a mixture of milk and chocolate.

Why the fat accumulates in the blood in these pathological cases of lipemia is not well understood. There is no proof that the body cannot oxidize the fat.

Saponification of fat (lipolysis) probably does not occur in the blood serum. The content in volatile fatty acids is sometimes determined by means of the "Reichert-Meissl number"; the content in oxy-fatty acids, alcohols and other constituents containing OH, by means of the so-called "acetyl-number."

Recently, attempts to study the blood-lipoids after removal of the cholesterin, by determination of the *iodin-number* (Hübl), which is a measure of the content in unsaturated fatty acids, have been made. Thus, J. H. King, working with H. Eppinger, has found that a parallelism exists between hemolytic processes and a high iodin-number (*Jodzahl*). The iodin-number falls after splenectomy; though the total fat-content of the blood rises. They found very high iodin-number in the blood in pernicious anemia, in cirrhosis of the liver, in hemolytic icterus, and in the stasis of myocardial insufficiency. Along with such studies of the iodin-number, it is desirable to keep tab on the number of formed and destroyed

red corpuscles. Eppinger tries to judge of erythrocyte destruction by following the urobilin in the stool by means of the spectral-photometric method of Charnass. High urobilin-values were found in primary anemia, hemolytic icterus, malaria, lead poisoning, and pneumonia, while low values were met with in carcinoma and in anemia from postpartum hemorrhage. These urobilin-values fall enormously after splenectomy, in hemolytic icterus and in pernicious anemia. As a result of these studies, Eppinger believes that a group of cases can be distinguished in which there is increase of the normal spleen function (*Hypersplenie*), and that they are improved by splenectomy. The body tries to overcome hypersplenia by increased activity of the bone-marrow, and by fibromatous changes in the spleen. He thinks that when hemolysis is demonstrably increased, therapy should not be directed toward increasing the function of the bone-marrow, but to decreasing the splenic function, by splenectomy.

Carbohydrates.—Among the carbohydrates occurring in the blood are (1) *free glucose*, (2) the so-called *"virtual" sugar* of Lepine (not accessible to direct estimation, but determined after hydrolysis), (3) *glycuronic acid*, (4) *fructose*, and (5) *animal gum*. In normal adults the sugar-content of the blood is very constant, and varies but little with the food-intake. On exact analysis, amounts a little below 0.1 per cent are usually found.

An increase of the sugar in the blood is known as *hyperglycemia*. This is met with, continuously in diabetes mellitus, and temporarily under various conditions in which glycosuria occurs; it is probably due to accelerated mobilization of the liver glycogen. After blood is drawn, the sugar gradually disappears from it, the *glycolysis* depending upon a glycolytic ferment, which is present not only in the blood serum, but also in the various organs. It is not an oxidase.

Extractives.—The extractive substances of the blood are divisible into (1) those containing nitrogen and (2) those free from nitrogen.

Of the *nitrogen-containing extractives* (included above with the "rest-nitrogen") may be mentioned, urea, carbaminic acid, kreatin, uric acid, hypoxanthin, the amino acids, and the proteinic acids (antioxyproteinic acid, and alloxyproteinic acid).

The normal amount of *urea* in the blood has been estimated to be 0.1-0.2 per cent, though during digestion it may reach 0.61 per cent. In pathological states, especially in the nephropathies, the amount of urea may be much increased. There is no relation, however, between the amount of urea and uremic states. Important information can, however, be gained by considering the relation of the urea in the blood to that in the urine (see Ambard's Coefficient, Part X).

In all cases in which there is increased proteolysis in the body, the urea content of the blood may be increased. In hepatic insufficiency, the urea of the blood, and of the urine, may be reduced, in which event its place seems to be taken by amino acids.

The *uric-acid* content of the blood is normally very small. It is difficult to detect amounts less than one milligram in 100 c.c. (Magnus Levy), and, ordinarily, less than this is present in normal blood, though after a meal rich in purins (sweetbreads), as much as 5 milligrams may be present in 100 c.c. (Weintraud).

An increase of the uric acid in the blood is known as *uricacidemia*. This is always present in gout, as was long ago shown by the thread-test of Garrod. A uricacidemia is also met with whenever many cell nuclei are undergoing degeneration in the body (resolving pneumonia; leukemia; x-ray therapy of spleen, bone-marrow or lymph glands).

Amino acids occur in normal blood on their way to the various tissue cells. Normally, the amounts of free amino acid are probably small, though J. J. Abel, by his "artificial-kidney" method in animals, has been able to separate large quan-

tities of amino acids by keeping the circulation going through the dialyzer for several hours. Abderhalden has also isolated considerable quantities of amino acids from the blood by studying an enormous quantity (a barrel full) at one time. We shall doubtless, later on, hear more about the examination of the amino acids of the blood, but, as yet, the methods are not available for clinical purposes.

A certain amount of *ammonia* is normally present in the blood (1 milligram in 100 c.c.). In acidosis, the ammonia is caught up out of intermediary metabolism and is not changed, as in normal conditions, to urea in the liver, but is used to neutralize the abnormal acids. In uremia, too, there seems to be an ammoniemia.

Among the *nitrogen-free extractives* are included lactic acid, ethyl alcohol, glycerin, acetone, oxybutyric acid (important in diabetic acidosis), indoxyl, indol, and skatol, and the coloring matters (lipochromes).

Inorganic Salts.—The inorganic salts of the blood can be studied by analyzing the ashed blood. It must be remembered that, on combustion of protein, sulphuric acid and phosphoric acid are formed, so that at least a part of these substances, and perhaps other constituents of the ash (alkali), are to be referred to this source. Again, it is possible that the newly formed H_2SO_4 and H_3PO_4 may have driven off some HCl and H_2CO_3. A study of the ash may, therefore, be somewhat deceptive as regards the kinds of inorganic salts and their quantity, as far as the serum is concerned. For clinical purposes, the amount of *sodium chlorid* in the blood is perhaps the most important value to be determined.

The *iron*-content of the blood depends upon the hemoglobin content. It is believed that in each hemoglobin molecule there is one atom of iron. The iron-content of hemoglobin is said to be 0.336 per cent (Hüfner).

The *formed elements of the blood*, separate from the plasma, are also being studied chemically for their protein, fat, carbohydrate, extractive and inorganic constituents.

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(j) The Ferments of the Blood

Recently, a good deal of attention has been paid to the content of the blood in various ferments. Among the ferments believed to exist in the blood are the following:

A. Carbohydrate-Splitting Ferments:

1. Diastase, which liquefies and hydrolytically splits starch or glycogen, with formation of dextrin, maltose, and grape sugar.
2. Glycolytic ferment, which splits glucose, though the products of the cleavage are not known. It is best demonstrated in the blood by the method of Rona and Doeblin.

B. Lipases.

1. Lipase. It can sometimes be demonstrated in the blood by the monobutyrin method, or by the lecithin method.
2. Cholesterase. This can be demonstrated by the method of J. H. Schultz.

C. Proteolytic Ferments.

1. Leukoproteases. These are known to occur in the polymorphonuclear neutrophilic leukocytes.
2. Antitrypsin. This also occurs in the blood and will inhibit the effects of trypsin. Although an enormous amount of work has been done with the antitrypsin reaction, about all that can be positively said, from the clinical standpoint, is that if one find a normal, or a diminished, antitrypsin-content in the blood, the presence of carcinoma in the body is improbable.

D. Nuclein Ferments.

1. Nucleases. These split nucleic acid into nucleotides and nucleosides (Levene).
2. Deamidases. These are ferments that split adenin and guanin; they are known as adenase and guanase.
3. Oxypurinases. And, finally, ferments that oxidize the oxypurins (xanthin, uric acid), such as xanthinoxidase and uricoxidase or uricase are known to occur; in man, uricase is not met with. (See Part XIII.)

E. Oxidases.

1. Peroxidases. The whole blood, owing to the presence in it of polymorphonuclear leukocytes, yields positive guaiac and phenolphthalein reactions, owing to oxidation of the guaiacon acid to guaiac blue, and the phenolphthalin in alcoholic solution to phenolphthalein (Eric Meyer). Lymphocytes do not yield this reaction.
2. Phenolases. Oxidases known as phenolases also bring about the synthesis of indophenol blue (Winkler, W. H. Schultze).

3. Catalases. These ferments can split hydrogen peroxid into molecular oxygen and water without any accompanying oxidation process. Such catalase is present in variable amount in all animal and vegetable tissues. Its presence has been demonstrated in the blood serum, though its physiological significance is entirely unknown. Many clinical investigations have been made with the methods of measuring catalase-activity (*q. v.*), and perhaps some diagnostic and prognostic value can be maintained for them. The catalases have been studied especially in the clinic in which I work by Winternitz and Meloy, and by Winternitz, Henry and McPhedran.

It has been found, for example, that the toxemias of pregnancy are separable into two classes as regards catalase examinations. Those without renal involvement show no change in catalase; those with renal insufficiency show a diminution of catalase activity.

In typhoid, late in the disease, there is a gradual fall in catalase activity. In labor pneumonia, a slight decrease was noted.

In hyperthyroidism, there was some increased catalase activity; in hypothyroidism, a diminution.

In well-compensated nephropathies, the catalase activity was nearly normal, but in uremic states it was much decreased. In prostatic hypertrophy, causing urinary obstruction, a decrease of activity was noticed. In diabetes mellitus and in the cardiopathies, no marked changes were observed.

Despite the large amount of work done with catalases, testing for them is, as yet, clinically unimportant.

F. Abderhalden's Reaction.

During the past three years, an unprecedented activity in ferment work has been characteristic of the clinical laboratories of Germany, and, to a certain extent, of this country, owing to the introduction of Abderhalden's "dialysis procedure." The method is given elsewhere in this volume (*q. v.*). It is too early yet to speak positively regarding its value, though it seems to be of real help in the early diagnosis of pregnancy, and may prove to be of value in diagnosing organic disease in all parts of the body.

2. Brief Review of the Formed Elements of the Blood

By the formed elements of the blood we mean (a) the red blood-corpuscles, (b) the white corpuscles, (c) the blood platelets and (d) the blood dust.

(*a*) *The Red Blood-Corpuscles* (*Erythrocytes*)

The red blood-corpuscles are by far the most numerous of the formed elements of the blood, the *number* in man amounting to about 5,000,000, and in women to about 4,500,000, per cubic millimeter. In *shape*, these corpuscles, like those of the higher animals generally, are round, non-nucleated, biconcave disks, thus differing from the red corpuscles of birds and the lower animals, which are nucleated.

The Size of the Red Corpuscles.—The average diameter of a red blood-corpuscle is 7 μ, the average thickness 2 μ.

The *color* is due to the presence of hemoglobin. Examined fresh, the red corpuscles look yellowish, but have a slightly greenish tint. In the thinner centers of each disk, the color is paler. In dried and stained specimens, the red corpuscles show an especial *affinity for acid dyes* (*e. g.*, eosin, acid fuchsin, orange G), a property due, also, to their hemoglobin content.

The red corpuscles, both inside and outside the blood vessels, tend to form coinlike rolls, or *rouleaux* of 20 or more cells. This rouleaux formation, or sympexis, seems to depend upon surface tension, though some think it due to a kind of agglutination.

The *internal structure* of the red corpuscles has not yet been fully determined. The contained hemoglobin dissolves out in water, leaving a *stroma* that is insoluble. The histological organization of this stroma is disputed. No definite framework has been made out in it, even with the use of ultra-violet light, but certain facts make it probable that it is not homogeneous but possesses some structure. Some authors assert that they can make out a spherical body, which they think is the remains of the nucleus of the red corpuscle; but this "nucleoid theory" has not met with general acceptance. Certainly, remains of nuclei which take chromatin stains, are occasionally visible, especially under pathological conditions (*vide infra*).

When the red corpuscles are placed in water, the hemoglobin dissolves out; the blood becomes "laked." In such laked blood, one sees "*shadows*" of the hemoglobin-free corpuscles; these shadows, in contrast to the hemoglobin-containing corpuscles, show an affinity for basic dyes (*e. g.*, methylene blue).

The maximal *hemoglobin-content* of human blood is 13.77 grams of hemoglobin in each 100 c.c. The hemoglobin consists of (1) the protein known as *globin* (a colorless body resembling histone) and (2) the iron-containing *hemochromogen*.

Hemoglobin unites very easily with oxygen to form *oxyhemoglobin*. It can form this union more or less independently of the partial pressure of oxygen. If it were not for this property, we should have much more difficulty in breathing in mountain altitudes, in a balloon, or in an aeroplane, than we do. The red corpuscles act as *oxygen carriers* from the lungs to the tissue cells, a function that is doubtless facilitated by the absence of

nuclei in the corpuscles. Each gram of hemoglobin is capable of carrying 1.34 grams of oxygen.

Normally, each single red corpuscle contains a definite, constant amount of hemoglobin. The total 5,000,000 red corpuscles contain an absolute amount of hemoglobin, which corresponds, maximally, as we have seen, to 13.77 g. to every 100 c.c. of blood. This corresponds to 100 per cent on the scale of some of the instruments used for determining the hemoglobin-content of the blood (hemoglobinometer, hemometer). If, on making a count of the red blood-corpuscles, we find a normal number of red corpuscles per cubic millimeter (*i. e.*, 100 per cent of the normal number of corpuscles), and, on making a hemoglobin estimation, we find 100 per cent of the normal amount of hemoglobin, we say that the *individual corpuscular content in hemoglobin* is normal, or that the *color-index* is normal, for by the color-index we mean the quotient, $\frac{\text{percentage of hemoglobin}}{\text{percentage of normal red count}}$; in this case the quotient, $\frac{100 \text{ per cent}}{100 \text{ per cent}} = 1$, and 1 is thus the normal color-index. In pathological conditions, this color-index may be less or greater than 1; it may be as low as 0.5 or as high as 1.5. Such low indices and high indices are of great help in clinical diagnosis. See Determination of Color-Index, farther on.

The rapidity with which oxyhemoglobin is reduced by the tissue cells depends upon the *oxidative energy of the tissues;* methods of determining this oxidative energy have been worked out (spectroscopic examination of finger-tip or ear lobule, after mechanical interruption of the circulation).

The red blood-corpuscles may have another important function; namely, the *absorption of certain light rays* by their hemoglobin. It is obvious that the whole body is, beneath the epidermis, surrounded by a "red mantle" that will permit the penetration of certain rays of light only, the hemoglobin absorbing all light rays except the chemically-inactive red rays. This subject deserves further study.

The content of the red blood-corpuscles in *lipoid substances* (lecithin and cholesterin) may prove, later, to be of great clinical importance. Preston Kyes has shown, for example, the importance of lecithin in the red blood-corpuscles in the hemolysis due to cobra-venom. It has been asserted, also, that the hemolytic effect of saponin, of chloroform, and of other substances, depends upon their capacity to alter the lipoid membranes of the red corpuscles. The subject attains to special interest on account of the newer theories regarding the origin of the severe hemolytic anemias.

In pathological states, the R. B. C. may be diminished in number (oligocythemia), or in hemoglobin-content (oligochromemia) or both. The *shape*, the *size*, and the *appearance in dried and stained smears* may all deviate from the normal.

Normally, the red corpuscles, though round, biconcave disks, are very elastic structures, and can change their shape easily. Under pathological conditions, very remarkable distortions of the erythrocytes are seen—long, pear-shaped forms, branched forms, etc., known as *poikilocytes*. In poikilocytosis, the red corpuscles may resemble parasites very closely, and have even been designated 'pseudoparasites.' The more severe an anemia is, the more marked the poikilocytosis, as a rule, but poikilocytosis is not confined to any one form of anemia. As a general rule, however, when poikilocytosis is present to any marked degree, it is much more suggestive of pernicious than of secondary anemia. The cause of the poikilocytosis is unknown.

The *size* of the red corpuscles is, under normal conditions, tolerably constant, but in certain anemias, especially in pernicious anemia, great differences in size are met with; very small forms (*microcytes*) and very large forms (*macrocytes*) appear. (See Measurements of the R. B. C.) Such inequality of size of the red corpuscles is known as *anisocytosis*. It is probable that the macrocytes are derived from megaloblasts and that the microcytes are derived from abnormally-small erythroblasts, though it is possible that they may also arise by fragmentation of normal-sized red cells or of macrocytes.

While the normal red cells are typically *acidophile* (oxychromatic) in stained preparations (see Stained Smears), a deviation from this behavior may be met with under pathological conditions, the cells taking up basic dyes either diffusely, so as to stain in eosin-methyl-blue in a gray-violet tone, instead of pink, or in simple methylene blue taking a bluish tint instead of the light green of the normal corpuscle. Such staining is known as polychromatic staining, and the condition in the red cells as diffuse *polychromasia*. Such polychromasia is usually a sign of the youth of the red cells, inasmuch as the protoplasm of the normoblasts stains polychromatically. Polychromasia may also appear, sometimes, as a degenerative sign in senile red corpuscles.

In lead poisoning, and in certain other conditions, a *basophilic granulation* of the red corpuscles is met with. This will be described more fully, along with other abnormal features, when we take up the study of stained blood smears.

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(*b*) *The White Blood-Cells* (*Leukocytes*)

Discovered in 1770 by Hewson, and given importance in pathology by Virchow's studies on leukemia and Cohnheim's discovery of the emigration of the leukocytes in inflammation, it was not until Ehrlich devised

his *elective staining methods* of dried smears of blood that knowledge of the leukocytes could attain to its modern development. By means of Ehrlich's methods and of other methods devised later, it has been found possible to subdivide the white blood-corpuscles into definite classes.

The *grouping of the white cells in classes* depends upon (1) whether, or not, granules are present in the protoplasm, and how these granules stain, (2) the structure and form of the nucleus, and (3) differences in the chemical composition and the fermentative powers of the cells.

By these methods the normal white blood-cells are divisible into (1) *neutrophilic polymorphonuclear leukocytes*, (2) *eosinophilic polymorphonuclear leukocytes*, (3) *basophilic polymorphonuclear leukocytes*, (4) *lymphocytes* (small and large), (5) *large mononuclear* and (6) *transitional* forms.

A somewhat different classification is coming into vogue, especially in the Southern and Middle Western States, in which the terms *endotheliocytes* and *splenocytes* are used; this method of classification will be described under Differential Counts of the White Cells.

The details of the morphology of these different forms will be considered under the methods of differential staining, where also the *pathological varieties of white blood-cells*, not normally present in the blood, but which enter the blood sometimes under pathological conditions, will also be described. These pathological varieties include (1) *myelocytes* (neutrophilic, eosinophilic and basophilic), (2) *myeloblasts*, (3) *lymphoblasts* and (4) *plasma cells*.

On *counting the white blood-cells*, it is found that normal blood contains 7,000 to 8,000 per cubic millimeter. This number is subject to marked variations, even under normal conditions.

Under pathological conditions, the number of the white cells may be greatly increased, or markedly diminished. When there is an increase in the total white-cell count, it is important to know what varieties of cells are responsible for the increase. When it is the polymorphonuclear neutrophils that are increased in number, we speak of a *polymorphonuclear leukocytosis;* when it is the eosinophils that are increased, we speak of an *eosinophilia*, or of an *eosinophilic leukocytosis;* when it is the lymphocytes, of a *lymphocytosis*. When the total number of white cells is diminished, the condition is known as leukopenia. When pathological varieties of cells (myelocytes, myeloblasts, or lymphoblasts) enter the blood in large numbers, increasing the total number of white cells, we are dealing with *leukemia*.

All these conditions (leukocytoses, lymphocytoses, leukopenias, leukemias) will be subjected to a finer analysis further on.

The relative proportions of the normal white cells to one another are tolerably constant in normal blood; thus, in healthy medical students in the

Johns Hopkins Medical School, the polymorphonuclear neutrophils average 64.2 per cent, the polymorphonuclear eosinophils 2.8 per cent, the polymorphonuclear basophils 0.6 per cent, the small mononuclears (lymphocytes) 22.5 per cent, the large mononuclears and transitionals together 10.8 per cent (Sydney Miller). The *absolute numbers* in the same students average as follows: P. M. N. 4,780, P. M. E. 205, P. M. B. 49, S. M. 1,656, L. M. and T. 755, per cubic millimeter.

In studying the white cells of the blood, clinically, it is important to know whether or not there is a change, either in the absolute number of each of these different varieties present per cubic millimeter, or in the relative proportions of the different kinds.

The *functions of the white blood-cells* are not so clear as those of the red corpuscles. We know that the white cells play an important rôle in normal digestion, in the combating of infections, in inflammations, and in the absorption of inflammatory exudates in the serous cavities, lungs and elsewhere.

The *phagocytic activity* of the white cells has been well recognized since Metchnikoff's studies. Phagocytic digestion is due to intracellular ferments. Thus the polymorphonuclear neutrophils, or microphages, contain microcytase; the large mononuclears, or macrophages, contain macrocytase.

These *ferments of the leukocytes* have recently been made the object of especial study. The polymorphonuclear neutrophils contain a proteolytic ferment (leukoprotease), which seems to be absent from the lymphocytes. The latter cells are capable of autodigestion, but seem to be incapable of digesting foreign tissue.

The granular leukocytes contain also oxidases (phenolase, peroxidase); the lymphocytes do not. Since the granular leukocytes arise from the bone-marrow, it is possible that cells derived from the bone-marrow (myeloid origin) can be distinguished from cells originating in the lymph glands and other lymphoid tissues (lymphadenoid origin) by means of their ferment production.

(*c*) *The Blood Platelets*

In *size*, *shape*, and *appearance* these bodies are small, oval particles, about 3 μ in diameter, consisting of two parts, a refractive internal mass of protoplasm, surrounded by a delicate, less refractive, protoplasm. This internal mass stains intensely in basic dyes, and in iron hematoxylin but does not consist of nuclear substance. The *origin* of the blood platelets, in all probability, is by the "pinching off" of minute particles of the protoplasm of the megakaryocytes of Howell in the bone-marrow (J. Homer Wright). I have seen Wright's specimens demonstrating this; they were to me very convincing.

The normal *number* of platelets is about 250,000 per cubic millimeter. The number is altered in various diseases, as will be pointed out later.

The *biological and chemical properties* of the blood platelets are as yet but poorly understood. They possess slight ameboid movement; they are very sensitive to changes in the potential alkalescence of the blood, and also to changes in the tension of the carbon dioxid (Deetjen). They contain peptid-splitting ferments, and also iodophil substances.

The blood platelets probably play an important rôle in the process of coagulation of the blood. They have been shown to contain thrombogen (Morawitz), and, very recently, Bayne-Jones has demonstrated that they cannot only give rise to prothrombin, but can also liberate a substance capable of neutralizing antithrombin.

It is well known that in thrombosis of the blood vessels *intra vitam*, and in the formation of vegetations on the heart valves in endocarditis, the blood platelets appear in agglutinated masses, the fibrin appearing later.

(*d*) *Hemoconia*

The particles of so-called *"blood dust"* (hemoconia) do not consist of blood platelets. They do not correspond, in all probability, to any one single kind of body. They appear as minute, round, dancing granules (Brownian movement) on examination of the fresh blood. Some of them are probably extruded leukocyte granules.

3. Brief Review of the Birth, Duration of Life, and Death of the Formed Elements of the Blood

(*a*) *The Birth of the Red Blood-Corpuscles* (*Erythropoiesis*)

The red corpuscles of the blood (erythrocytes) are derived from the nucleated red cells (*erythroblasts*) of the bone-marrow. In adults, these erythroblasts exist only in the red marrow of certain bones (vertebrae, ribs, scapulae). In this red marrow, the erythroblasts, or *normoblasts*, as they are sometimes called, are present in large numbers. They are about the size of ordinary red blood-corpuscles, but contain a *nucleus*, rich in chromatin, arranged in young normoblasts somewhat like the spokes of a wheel. As the normoblasts grow older, this nuclear structure changes; the chromatin becomes more evenly distributed throughout the nucleus, which begins to contract and to become pyknotic; then it begins to fragment (karyorrhexis), and, gradually, it dissolves up entirely, within the cell. The view formerly held, that the erythroblast gets rid of its nucleus by extruding it, has been given up.

The *protoplasm* of the erythroblasts is not so acidophil, on staining, as that of the adult red corpuscle, but, instead, takes up some of the basic as well as some of the acid dye, that is, it stains polychromatically. The

younger the erythroblast, the more marked the tendency of its protoplasm to polychromasia.

Before leaving the bone-marrow to enter the blood, the erythroblasts normally lose their nuclei. If specimens of bone-marrow be examined, many of the erythroblastic cells that have just dissolved up their nuclei can be recognized by their polychromasia, their protoplasm still staining in a way that reveals their youth as contrasted with the age of the non-polychromatophilic adult red corpuscles.

In the *embryo*, the red blood-corpuscles are derived from another form of red cell, the so-called *megaloblast*. These megaloblasts are twice as large as normoblasts, and have a very different kind of nucleus, much poorer in chromatin, and of a more delicate structure. Now and then, a megaloblast can be seen in normal bone-marrow. In severe hemolytic anemias, these megaloblasts may reappear in large numbers in the bone-marrow; in such cases, they, like the normoblasts in the posthemorrhagic anemias, sometimes go over into the circulating blood.

(*b*) *The Duration of Life and the Death of the Red Blood-Corpuscles*

After they enter the blood from the bone-marrow, the red corpuscles have a *short life*, averaging about a month (Quincke). If this estimate be correct, then about 1/30 of all the red corpuscles in the blood are destroyed, and as many new ones formed, every day.

As soon as a red corpuscle has reached a certain age, or has, from any cause, become slightly injured, it is removed from the circulation; it is caught by one of the large mononuclear macrophages of the internal organs, chiefly the spleen, but to a less extent, also, the bone-marrow and liver. When large numbers of red corpuscles are suddenly injured, this phagocytic activity of the spleen becomes enormously increased and the spleen rapidly enlarges (*spodogenous splenic tumor*). As the corpuscles are digested within the phagocytes, their iron is separated out as *hemosiderin*, and the iron-content of the spleen and liver increases. Undoubtedly, a good part of this iron is used over again, in the bone-marrow, in the manufacture of new hemoglobin. The non-ferruginous part of the hemoglobin from the broken-down corpuscles is used up in the liver in the manufacture of bile pigments.

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(*c*) *The Regeneration of Red Blood-Corpuscles*

The bone-marrow must stand under some precise regulatory influence that keeps its activities balanced, for, normally, the manufacture of new red corpuscles in the marrow goes on *pari passu* with the destruction of the "senile" and "decrepit" red corpuscles by the hemophagocytic organs.

When there is an unusually rapid diminution of red cells (by hemorrhage, by hemolytic intoxication), the bone-marrow responds promptly, by an *accelerated erythropoiesis,* and, if the injury has not been too great, normal conditions are quickly restored. If the blood destruction has been severe, or if such losses are frequently repeated, anemia develops, and the bone-marrow begins to pour out *immature forms* of red blood-corpuscles (polychromatic corpuscles, normoblasts, and, in certain instances, megaloblasts). Sometimes, great numbers of normoblasts, within a very short period, are thrown into the circulating blood (so-called *blood crisis*). These immature forms are evidence of the existence, still, of a lively regenerative power on the part of the bone-marrow. If, in a marked anemia, no such regenerative forms appear in the blood, it is evidence of an inability of the bone-marrow to respond to erythropoietic stimuli; such an anemia is known as an anemia due to decreased blood-formation (*e. g.,* aplastic, or aregeneratory, anemia).

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(*d*) *The Birth of the White Blood-Corpuscles* (*Leukopoiesis*)

In adults, the white blood-cells are derived partly from the bone-marrow (*myeloid origin*), partly from the lymph glands, spleen, and other lymph-adenoid tissue of the body (*lymphadenoid origin*). The neutrophilic, eosin-

ophilic and basophilic leukocytes, in other words, all the granular leukocytes, are of myeloid origin. The lymphocytes are of lymphadenoid origin. The origin of the large mononuclear and transitional forms is not clear; it may be that they are derived from the endothelial cells of the spleen and the lymph glands, though the evidence at present favors a myeloid origin.

The *myeloid elements*, that is, those derived from the bone-marrow, come from the *myelocytes* situated there. Corresponding to the three varieties of granular leukocytes, there are, in the bone-marrow, at least three varieties of granular myelocytes; namely, neutrophilic, eosinophilic and basophilic myelocytes. Under ordinary conditions, these myelocytes increase in number by karyokinetic subdivision, but they also arise from nongranular cells in the marrow that resemble in many respects large lymphocytes, but which, in reality, are distinguishable from lymphocytes; these are the *myeloblasts* of Naegeli.

The *lymphadenoid elements* are derived from mother cells in the lymphadenoid tissues of the body. In the lymph follicles of the lymph glands, in the Malpighian follicles of the spleen, in the lymphadenoid tissue of the thymus and of the intestine, and in the small foci of lymphadenoid tissue scattered through all the organs, there is a characteristic arrangement of small round cells lying in meshes of a reticular framework. The smaller of these cells are indistinguishable from the small lymphocytes of the blood. The larger cells in the germinal centers (*Keimcentra*) resemble the large lymphocytes of the blood, and are probably the parent cells of the small lymphocytes, since, in hyperplasia of the lymph glands, there is marked activity in these germinal centers with karyokinetic figures there. The mother cell of these lymphocytes is the so-called *lymphoblast*. The lymphoblasts and the large lymphocytes resemble somewhat the myeloblasts of Naegeli, but they are distinguishable from them morphologically, chemically, and biologically.

As will be seen, I am an adherent of the dualistic doctrine of Ehrlich as regards the myeloid and lymphadenoid origin of the different kinds of white blood-cells. It is true, there is some evidence that favors the unitarian view of a common origin of all the white cells, championed by Pappenheim, Maximow and Hirschfeld; but it seems to me that the evidence brought forward originally by Ehrlich, and supplemented later by Naegeli, Schridde, Winkler, Schultze, Morawitz, and others, makes the dualistic doctrine more probable. The crux of the question lies in the nature of the so-called myeloblasts of Naegeli, found in the marrow. If these are really specific myeloid cells that can be distinguished both morphologically and chemically from lymphoblasts and large lymphocytes, then the dualistic doctrine is upheld; but if the myeloblasts of Naegeli are identical with large lymphocytes and lymphoblasts, then one would have to adopt the unitarian doctrine. There is one possibility that, as far as I know, has not been adequately considered in the polemic bibliography; namely, that, in the marrow, we may have not only true myeloblasts (myeloid in origin), but also a few lymphoblasts arising in the marrow, wholly similar to the same cells of lymphadenoid origin elsewhere in the body. Since we know that islands of lymphadenoid

tissue are scattered through all the organs, is it not reasonable to suppose that there are some such islands in the bone-marrow as well? If this view of mine be correct, then we should be able, by careful analysis, to distinguish among the cells resembling large lymphocytes and myeloblasts in the marrow, two definite varieties, one having the morphological and chemical characters of lymphocytes (or lymphoblasts), and the other having the morphological and chemical characteristics of myeloblasts.

Undoubtedly, under pathological conditions (leukemias, bone-marrow tumors, etc.), foci of extramedullary leukopoiesis of myeloid type, may appear in the spleen, liver, lymph glands and connective tissue, but such foci are entirely different from any lymphadenoid leukopoiesis that occurs normally in the same situation; in other words, such pathological extramedullary foci of multiple leukopoiesis represent a return to early conditions (*q. v.*).

(*e*) *The Duration of Life and the Death of the White Blood-Corpuscles*

How long a white blood-cell can live, we do not know. Since the white cells are nucleated cells, it is conceivable that they may have a longer life than the red corpuscles, but their consistence is less tough, and their life may be short. Many of them are killed in the struggle with invading bacteria. In inflammatory exudates, the emigrating white cells often undergo solution by autolysis when the inflammation is over (*e. g.*, in croupous pneumonia). It seems likely that the older white cells do not disintegrate in the circulating blood, but, like the senile red blood-corpuscles, are taken up by phagocytes in the splenic pulp and other organs, and there undergo intracellular digestion. The number of leukocytes undergoing such disintegration has an influence upon the amount of endogenous uric acid formed in the body. In leukemia, the endogenous uric acid is greatly increased, so much so, sometimes, as to give rise to gouty deposits.

A number of white blood-cells are constantly being lost from the body by way of the saliva, the nasal and bronchial secretions, the tonsils, the intestines and the urogenital tract.

(*f*) *The Regeneration of the White Blood-Corpuscles*

The regulatory mechanism for maintaining the leukocyte count of the blood at a normal level is as obscure as that for maintaining the normal number of red blood-corpuscles. As is well known, the number of white cells varies a great deal, daily, during normal life. There is an increase in the number of leukocytes in the blood after every meal (leukocytosis of digestion); in pathogenic infections there is a rapid increase in the number of leukocytes in the blood (leukocytosis of infection). In certain infections, however (*e. g.*, typhoid fever), the number of leukocytes in the blood is decreased (leukopenia of infection); in such cases, the bone-marrow contains fewer neutrophilic myelocytes than normal. It looks as though the leukopoietic functions, both myeloid and lymphadenoid, depend largely upon chemical stimuli.

(*g*) *The Birth of the Blood Platelets*

The bone marrow giant cells, or megakaryocytes (Howell), are among the largest cells that occur in the human body. They exist normally in red bone-marrow and occasionally a few of the smaller ones go over into the blood (after burns, certain infections, puerperal eclampsia, etc.). The nucleus of the megakaryocyte is very large and multiform. It is hollow, containing protoplasm inside it. The cells contain colonies of centrosomes (Heidenhain). The protoplasm within and near the nucleus is finely granular, the peripheral protoplasm being free from granules. Minute portions of the protoplasm are pinched off to form the blood platelets (J. H. Wright).

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(*h*) *The Blood Formation in the Human Embryo*

In early embryonic stages, the blood formation (hematopoiesis) occurs inside the blood spaces, which are bounded by the endothelial cells of the blood vessels. Here, a single variety of blood cell is, at first, met with; namely, the *primary erythroblast*, having all the characters of the megaloblast of Ehrlich (met with, later in life, in disease).

This intravascular blood formation gives place, a little later in embryonic life, to an extravascular blood formation, located chiefly in the liver (embryos 11-12 mm. long). The endothelial cells of the vessel walls give rise to (1) myeloblasts, (2) basophilic erythroblasts (the mother cells of normoblasts), and (3) giant cells or megakaryocytes. Still later in embryonic life (third month), the bone-marrow begins to develop an extravascular myeloid tissue, similar to that in the liver, and arising also from the endothelium of the blood spaces. In the embryo, the perivascular tissue all over the body, and especially that of the spleen, appears to contribute to blood formation, but, as the bone-marrow develops, hematopoiesis becomes more and more limited to this; blood cells cease to be formed in the spleen about the seventh month of fetal life, though some blood formation goes on in the liver up to the time of birth.

The endothelial cells of the lymph vessels, which give rise to the lymphoblasts and later to the lymphocytes, begin to be active, in the embryo, a little after the time when the liver takes on its blood-building function.

It will be seen that in the earliest embryonic stages the blood contains primary erythroblasts (megaloblasts) only. These give way gradually to secondary erythroblasts (normoblasts, and their mother cells), and then myeloblasts and non-nuclear erythrocytes (ordinary red blood-corpuscles) begin to appear in the blood. Their appearance is followed later by the entrance of lymphocytes into the blood, and only relatively late do the polymorphonuclear leukocytes (chiefly neutrophilic) come in. At birth, the blood contains almost exclusively non-nucleated red corpuscles with a few normoblasts, neutrophilic leukocytes and lymphocytes; only a few myeloblasts, neutrophilic myelocytes and eosinophilic and basophilic leukocytes are to be seen.

From birth on, the hemopoietic organs are divisible into two groups: (1) the myeloid tissues, responsible for erythropoiesis (red blood-corpuscles), for myeloid leukopoiesis (granular leukocytes), and for the formation of the blood platelets; and (2) the lymphadenoid tissues, responsible for lymphadenoid leukopoiesis (lymphocytes). The origin of the large mononuclears and the transitional forms is still obscure, but they probably come from the bone-marrow.

4. Comment on the Relative Importance of Different Methods of Examining the Blood

A very large number of methods of examining the blood have been employed, but only a few of these are, as yet, really of much practical significance. The others are either less important for diagnosis, or are required only in certain instances, especially where original investigations are being made. An attempt will be made here to separate the methods that, *at present*, are the more important from those of less importance, in order that the student may not be too much confused on approaching the subject for the first time. It is quite possible that as scientific clinical work advances, our views regarding the relative importance of the different methods will undergo radical changes.

I. The more important methods of examining the blood:

Under this heading may be considered:

(1) Technic of obtaining blood for examination.

(2) Quantitative estimation of the hemoglobin-content.

(3) Study of qualitative disturbances of the hemoglobin (spectral analysis).

(4) The counting of the red and white blood-corpuscles and the platelets.

(5) The microscopical examination of fresh, unstained blood.

(6) The study of the formed elements of the blood in dried and stained preparations.

(7) Certain bacteriological and serological examinations of the blood, including especially blood cultures, agglutination tests (Widal reaction), precipitin tests, complement deviation tests (Wassermann reaction), and fermentative tests (Abderhalden's reaction).

II. Methods clinically important, but less often used:

(1) The determination of the coagulation time of the blood.

(2) The determination of the viscosity of the blood.

(3) The determination of the resistance of red blood-corpuscles in anisotonic solutions.

(4) The determination of the sensitiveness of the red blood-corpuscles to iso-agglutinins (and iso-hemolysins).

III. Methods only occasionally employed in practical diagnosis:

(1) The estimation of the total amount of blood in the body.

(2) The estimation of the volume of the blood-corpuscles and of the plasma.

(3) The determination of the total solids in the blood, and the total water-content.

(4) The determination of the specific gravity.

(5) The determination of the alkalinity.

(6) The determination of the volume and of the tension of the gases in the blood.

(7) The determination of the osmotic pressure.

(8) The determination of the content of the blood in nitrogenous substances (total protein, globulins and albumins, non-protein nitrogen, ammonia, urea, amino nitrogen, amino acids, hippuric acid, total purins, uric acid, bile-pigments, indoxyl, indol, and skatol).

(9) Studies of ferments and of antiferments in the blood.

(10) The quantitative determination of the carbohydrates and of the acetone bodies in the blood.

(11) The quantitative determination of the fats, and fatty acids, in the blood.

(12) Determination of the inorganic constituents of the blood (total ash, Ca, and Mg, K and Na, Cl, Fe).

B. The More Important Methods of Examining the Blood

1. The Technic of Obtaining Blood for Examination

When only small amounts are desired, they may be obtained by puncture of the finger-tip or of the lobule of the ear. The former is the more satisfactory, as it is less influenced by the external temperature than the ear-lobule, and is free from fine hairs. The finger-tip should first be made actively hyperemic by immersing the hand for a few minutes in warm water, and then thoroughly cleansed with alcohol and ether and dried. As a blood-sticker, we may use Francke's needle, a Hagedorn needle, or one of the prongs of a sharp steel pen. Bass advises the use of a straight surgical needle, mounted on a cork; this is convenient, in that, when not in use, it is fitted into a small vial of alcohol and is thus kept constantly aseptic. Whatever sticker is used should be scrupulously clean, and, besides, should be rendered aseptic by alcohol, and dried, before the puncture is made. The sticker-point is brought quite close to the skin, and is introduced quickly, and only just far enough to draw blood. If the finger is hyperemic (as it should be made), a small drop will come out spontaneously; if it does not do so, a deeper stab should be made, for it is not permissible to press the skin to make the blood flow, as this mixes lymph with the blood and vitiates the test. The first drop that flows is discarded; after wiping it off, a second drop appears and this, or succeeding drops, may be taken up with a cover-glass and placed upon a warm slide for examination of the fresh blood, or smears may be made for dried and stained preparations. The same source can usually be used for obtaining the blood for hemoglobin estimations and for blood counting; but if the blood does not flow freely for each droplet desired, a fresh stab should be made.

Fig. 291. Francke's Needle.

The more extensive physical, chemical, and biological examinations of the blood require *larger amounts*. The blood should then be drawn with a sterile syringe, preferably a Record syringe, from a vein at the

bend of the elbow. The bend of the elbow is surgically sterilized in the ordinary way. A tourniquet, or bandage, is applied to the upper arm, just tight enough to interfere with the venous circulation though not with the arterial. The sterile needle of the syringe is plunged, in an oblique direction (from below, or from the side), into the vein and held in place by the examiner's left hand. Blood will at once begin to flow into the syringe. If exact chemical or physical examinations are to be made, the tourniquet should be removed after the needle has been introduced and before the blood is drawn, since stasis quickly alters the relative proportions of solids and water; neglect of this precaution has rendered worthless large numbers of examinations for viscosity, for volume-percentages, and for dried residue! Unfortunately, it is often difficult to get enough blood without stasis. Of course, if the blood be desired for making a bacteriological culture, or a Wassermann test, stasis does no harm and the tourniquet may be left in place until the syringe is full. When the desired amount of blood has been withdrawn, the needle is quickly pulled out, and the minute wound covered with sterile gauze. As soon as the syringe has been emptied of blood, it should be thoroughly cleansed with cold water before clotting takes place.

If *still larger amounts of blood* are required, aspiration into sterile Ehrlenmeyer flasks, or venesection, may be resorted to. The arm is prepared in the same way and blood may be allowed to flow freely from a cannula directly, or through a short rubber tube attached to it, into a receiving vessel; or, instead of puncturing with the hollow needle, the vein may be opened with a lancet and the blood caught in a vessel. It is difficult to secure a sterile specimen by the latter method. For ordinary bacteriological and serological examinations 20 c.c. of blood, easily obtainable by venous puncture with a Record syringe, will suffice; where 200 or 500 c. c. are desired, as in certain chemical examinations, venesection may be necessary. Blood obtained by cuts in the skin, or by cupping, is wholly worthless for chemical and physical examinations, owing to admixture with tissue juices. C. E. Simon has devised a method for taking blood directly from the arm vein into a sterile glass bulb, which is very convenient. For securing blood for a Wassermann test from children, Blackfan's method is satisfactory; it has been described in Part IV.

Reference

Bass* (*C. C.*).** *A practical, inexpensive, aseptic blood-sticker. Med. Rec., New York,* ***1910, *lxxvii, 538.*

2. The Estimation of the Hemoglobin Content of the Blood (Hb)

Marked deviations from the normal hemoglobin content will be recognizable by the experienced observer in the exuding blood droplet, but *never* should be inferred merely from changes in the color of the mucous membranes (*vide supra*). For clinical purposes, colorimetric methods of estimating the amount of hemoglobin are almost universally employed, on account of their simplicity. The most convenient clinical instrument that can at the same time lay claim to tolerable accuracy is Sahli's modification of Gower's hemoglobinometer. I can recommend it highly for general adoption by practitioners. The hemoglobin is changed into

acid hematin and compared with a standard solution of the same chemical substance.

The Fleischl-Miescher hemometer is an excellent instrument, as is also Dare's hemoglobinometer; these two instruments compare the color of the blood with grades of intensity of Cassius' golden purple.

It has been shown by Butterfield (1909), that the light extinction, the iron-content, and the oxygen-binding power of normal blood are constant values. Hence, we may also use methods that estimate these, in order to determine the percentage of Hb in the blood. The light extinction can be measured by spectral-photometry (Hüfner, König, Martens and Grünbaum); the iron-content can be determined by chemical methods (Butterfield's modification of Neumann's method; method of Autenrieth and Funk, 1912), and the Hb estimated therefrom; the oxygen-binding power (or the CO-binding power) can be determined by the ferricyanid of potassium method (Haldane and Barcroft, Plesch), or by colorimetric methods (Plesch's wedge-tube hemoglobinometer), and from this, recalling that an oxygen-capacity of 1.34 c. c. corresponds to 1 g. Hb, the amount of Hb can be easily calculated.

(*a*) *Sahli's New Hemometer*[1]

Principle.—The blood of the person to be examined is treated in known dilution with HCl to convert the Hb into acid hematin; the color of the brownish yellow fluid resulting is compared with that of a tube containing a standard brownish-yellow acid-hematin solution, which corresponds to a 1-per-cent solution of normal blood. Since the standard solution is really a fine suspension of acid hematin, a sediment will form after long standing. To guard against this error, a small glass bead is sealed in the tube, to facilitate thorough mixing of the suspension before it is used.

Technic.—A calibrated tube, of the same internal diameter as that of the tube containing the standard solution, stands parallel to the latter in a suitable black rack. The back of the rack is provided with a ground-glass plate, to make the light diffuse. For diluting the blood, an N/10 HCl solution is required. Just prior to the estimation, enough acid is placed in the calibrated tube to reach exactly to the mark 10, an amount corresponding to 2.0 c. mm. With the pipet accompanying the instrument, 20 c. mm. of blood are collected, and carefully blown out into the acid in the calibrated tube, the pipet being washed out thoroughly with the resultant mixture of acid and blood. The hydrochloric acid rapidly changes the red hemoglobin of the blood into a clear brown solution of hematin hydrochlorid. After the lapse of exactly one minute, water is cautiously added, drop by drop, until the color of the diluted blood is identical with that of the standard tube. The mark 100 on the standard

[1] Made by the optician Büchi, in Berne.

tube of the Sahli hemometer corresponds to a hemoglobin content of 17.2 grams per 100 c.c. of blood; blood containing this much Hb will, when diluted 200 times, give a reading of 109 in the Fleischl-Miescher instrument. Normal blood rarely contains so much Hb. As a rule, the readings on Sahli's tube, in normal blood, vary between 80 and 100 for men, and between 70 and 90 for women. The physiological variations are obviously large. The reading 100 on the scale must then be regarded as representing the maximal normal, not the average normal, amount of Hb. If there be less hemoglobin than normal, a color, equivalent to that of the control, will be reached at a lower dilution, and one can read off on the scale of the tube directly the hemoglobin value (Sahli).

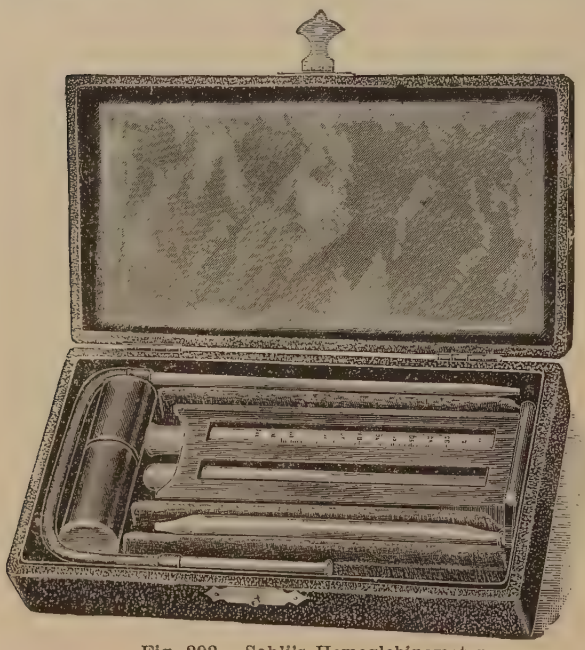

Fig. 292.—Sahli's Hemoglobinometer.

As an *arbitrary average normal* (though we are conscious of the wide variations within normal limits), especially for determining the color-index (*q. v.*), we may, with Naegeli, adopt the Hb-value 90 (Sahli), provided the red-corpuscle count is at the same time close to 5,000,000, and, microscopically, no anisocytosis is seen among the red corpuscles, and no inequalities in the hemoglobin content of the individual corpuscles (anisochromia); under such normal conditions the viscosity of the whole blood (η) is 4.2, that of the serum ($\eta = \eta_1$) is 1.8.

Sahli suggests that each worker with his hemometer establish an average normal for man and an average normal for women with the particular standard tube he owns, and the particular technic he employs, and then calculate a "corrected percentage" of normal. Thus if the average value for men be found to be 80, and his reading for the blood of a given person be 70, the "corrected percentage" of the latter will be $70/80 \times 100 = 87$. Similarly, if the average value for women be found to be 70, and the blood of a given woman yield a reading of 70, the "corrected percentage" for this blood would be $70/70 \times 100 = 100$.

Care should be taken to make sure that the hemometer has been and

remains correctly standardized. The standard tube should be kept in the dark, since all colored solutions, even the most stable, are altered by prolonged exposure to strong light.

(*b*) *The Fleischl-Miescher Hemoglobinometer*[1]

With this instrument, which is an improvement on the old, utterly unreliable, Fleischl hemometer, one compares the color of a small quantity of blood, diluted to a definite degree, with the color of a glass wedge of Cassius' gold purple. Blood is collected in a special pipet, like the mixing pipet of a blood counter. To make a 1:200 dilution blood is drawn up to the mark 1, followed by freshly prepared 0.1-per-cent sodium-carbonate solution up to the mark above the bulb; and the pipet is well shaken. To dilute 300 times, blood is sucked up to the mark 2/3; or 400 times, to the mark 1/2. An examining chamber, of a known depth, divided into halves by a median septum, which projects about ½ mm. above the borders, is placed

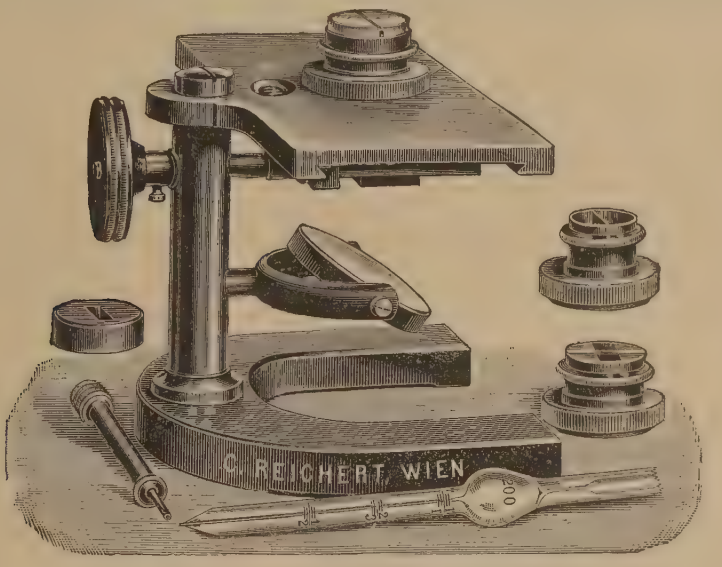

Fig. 293.—Fleischl-Miescher Hemometer.

on a central perforated stage. The diluted blood is placed in one half of the chamber, and distilled water in the other half, so that, in each case, a convex meniscus appears above the outer border of the chamber; a grooved cover glass can then be adjusted over the half-chambers, without mixing their contents. A diaphragm, with an opening 4 mm. wide, is next placed over the cover glass, the long axis of the opening being at right angles to the vertical partition of the examining chamber. The stand is so arranged that the colored wedge can, by means of a screw, be moved back and forth underneath the half of the chamber containing water. The reading is made in a dark-room by artificial light (preferably a small candle, placed 18 in. from the stand and to one side of it). The two divisions of the chamber are illuminated by means of a plaster-of-Paris reflector. The wedge is shoved to and fro until the water above it has the same tint as that of the diluted

[1] Made by C. Reichert, Vienna.

blood. The comparisons of the colors should be made by quick, rather than by gradual, changes, and the eyes should be frequently rested.

A series of not less than 10-12 readings are made for each specimen of blood taken, and two or three specimens of the same blood should be examined; for all these readings, the mean average is calculated. Besides the 15 mm. chamber, a 12 mm. chamber comes with the instrument; the diluted blood can be transferred to the latter, when it should yield readings only 4/5 as great as those obtained with the larger chamber. By reference, then, to a table of calibrations, which accompanies each instrument, one calculates the number of grams of hemoglobin per 100 c.c. of blood.

Sahli objects to the principle of the instrument, in that the color of the blood has to be compared with that of a different substance. On examining different instruments, the coloring of the wedge is found not to be uniform. Still, when a given instrument has been carefully calibrated, a skillful and experienced observer can make very accurate readings with the Fleischl-Miescher instrument; the error ought not to exceed 0.15 to 0.22 per cent by weight of the blood (Jaquet). The instrument is not likely to come into general use among practitioners, but every large hospital should have one for the control of other hemometers.

(c) *Dare's Hemoglobinometer*

In this instrument, the color of undiluted blood is compared with that of a graduated glass scale, colored with Cassius' gold purple. At 100 on the scale, the reading corresponds to 13.77 grams of Hb in 100 c.c. of blood.

Full directions for use accompany the instrument. Ralph Webster praises this instrument highly; it is less expensive than the Miescher, can be used in a light room, and yields reliable readings. But it is not a durable instrument, and is much more expensive than Sahli's hemometer.

(d) *Tallqvist's Hemoglobin Scale*

The hemoglobin scale of Tallqvist consists of a series of red colors, in chromolithograph, the values of which correspond to various percentages of the hemoglobin-content of normal blood. On a piece of white filter-paper is placed a drop of the blood to be examined; it is allowed to lose its humid gloss, but not to dry, and is afterwards compared with the colors of the scale, in good daylight. Most of the readings obtained are higher than they should be, though as a rough-and-ready method for the busy practitioner, the procedure has some value. If it do nothing more than lead the practitioner to realize the necessity of seeing the color of the drawn blood, as it appears on filter-paper, or on a towel, and to recognize the fallacy of trusting to the appearance of the visible mucous membranes, it is, in so far, praiseworthy.

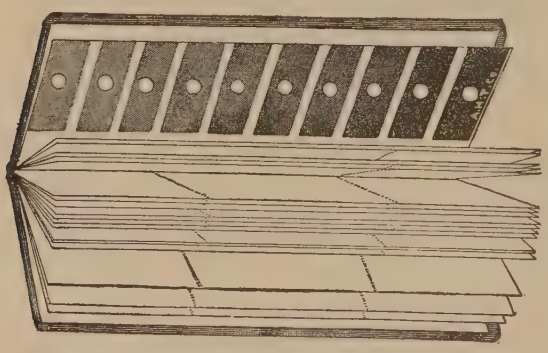

Fig. 294.—Tallqvist's Hemoglobin Scale. A Color Scale of Ten Tints, Ranging from Ten Per Cent to One Hundred Per Cent. (By courtesy of A. H. Thomas Co., Philadelphia.)

(e) *Light-Extinction Methods of Estimating the Hemoglobin (Spectralphotometric Determination)*

Two methods have been used.

(i) Hüfner's Spectralphotometer

For some time this was believed to be the most exact method of measuring the extinction coefficients, but the illumination of the instrument is bad, the form of the absorption vessel is unsuitable, and there are difficulties in exactly adjusting the instrument for equal illumination (Butterfield).

(ii) König's Spectralphotometer, as Modified by Martens and Grünbaum

This, according to Butterfield, is the instrument to use for very exact determinations of light extinction. The method is useful only for research work and will be found fully described in Martens and Grünbaum, in Butterfield, and in Brugsch and Schittenhelm (1914).

(f) *The Estimation of Hemoglobin by Means of Iron Determinations*

Here either one of two methods may be employed; (1) iron determination by Butterfield's modification of Neumann's method, and (2) colorimetric iron determination, according to Autenrieth and Funk.

(i) Butterfield's Modification of Neumann's Method of Iron Determination

Principle.—When a solution of zinc sulphate and phosphate of soda, in sulphuric acid, is made feebly ammoniacal and heated, all the zinc is precipitated as zinc ammonium phosphate. If the solution does not contain too large amounts of iron oxid, this is also precipitated at the same time. After dissolving the precipitate in HCl it is allowed to act upon KI; equivalent amounts of iodin are set free and determined titrimetrically (Neumann, 1902).

Butterfield has applied this procedure to the quantitative iron determination in human blood: 10 c. c. of blood, taken in a calibrated pipet, are emptied into a 500 c. c. oxidation flask; the pipet is washed thoroughly with water, the washings being added to the blood in the flask so that not a trace is lost. Concentrated sulphuric acid and nitric acid (equal volumes) are added, and the mixture is washed. The product is diluted, the excess of HNO_3 driven off, and, after cooling, the mixture is treated with Neumann's zinc reagent, neutralized with ammonia, and the precipitate just dissolved in a slight excess of ammonia. The solution is slowly heated to boiling, and kept gently boiling for half an hour, splashing being avoided by the addition of a few tetrahedra of platinum. The supernatant fluid, while still hot, is filtered off from the precipitate, and the latter is washed three times with hot water, until the filtrate, after acidulation with HCl, yields no sulphocyanid reaction. The precipitate is dissolved in dilute H_2SO_4, transferred to a large platinum crucible, and reduced with zinc. The complete reduction of 10 mg. iron requires three hours. The reduced solution is filtered through glass-wool, which is washed with H_2SO_4 into a beaker and titrated with $\frac{N}{100}$ permanganate solution from a Gay-Lussac burette. Before each determination, the permanganate is standardized against thiosulphate of known titer. The titer of the thiosulphate is controlled by $\frac{N}{100}$ potassium bichromate.

(ii) Colorimetric Determination of the Iron in the Blood (Autenrieth and Funk)

Only 25 c. mm. of blood are required. This amount is placed in a clean platinum crucible, the pipet being washed out with water two or three times, and the washings added to the blood. Evaporate to dryness, wash cautiously over a small flame until all carbon particles have vanished; add 0.5 grams potassium bisulphate; heat, shaking the crucible gently at first, vigorously later, until almost all the excess of potassium bisulphate has been decomposed, and only a little white vapor of anhydrous sulphuric acid passes off. Allow to cool, dissolve in a little $\frac{N}{2}$ HCl, warm cautiously; pour the solution (without loss) into a 25 c. c. graduate; wash the platinum crucible 2 or 3 times with a little $\frac{N}{2}$ HCl, and add these washings to the fluid in the graduate; dilute with the same acid until the total volume of the solution amounts to 6 c. c.; then add 6 c. c. of sulphocyanid of potassium solution, and also (exactly) 10 c. c. of pure ether. Cool thoroughly, and shake vigorously. Pour off the clear ether solution from the graduate, and compare it, colorimetrically, with a calibrated iron wedge, from which can be read off the amount of iron in the 10 c. c. of ether solution; this corresponds to the amount of iron-content in 25 c. mm. of blood. If this value be multiplied by 4,000, we have the amount of iron in 100 cm. of blood. One can make his colorimetric iron wedge himself, according to Autenrieth's description, or a carefully calibrated iron wedge can be purchased (Hellige & Co., Freiburg).

The method requires absolute cleanliness, and absolutely pure iron-free reagents. All vessels used in the process are best cleaned with $\frac{N}{2}$ HCl, then washed with alcohol and ether, and dried. Iron-free HCl is obtained by adding, drop by drop, concentrated H_2SO_4 to smoking HCl. This drives off pure HCl gas, which is collected in ice-cold distilled water, free from iron. For other details of the method, the original article should be consulted.

(g) *The Estimation of Hemoglobin by Determining the Oxygen or the Carbon-Monoxid Combining Power of the Blood*

Here two principal methods have thus far been used: (i) the ferricyanid method, and (ii) the carbon monoxid method.

(i) Ferricyanid Method of Determining Oxygen-Capacity (Haldane and Barcroft)

This method permits of very exact oxygen analysis with the use of very small amounts of blood, even as little as 1 c. c. The method is technically easy to learn.

Principle.—If blood be laked, the oxygen united with the hemoglobin can be set free, quantitatively, by ferricyanid of potassium. The gas is collected, the pressure measured by means of a water manometer, and the temperature and volume noted. The error is not more than 3 per cent. This method is entirely suitable for clinical researches on the blood gases.

After the determination of the amount of oxygen, the amount of CO_2 present can be measured, if desired, by adding tartaric acid.

The hemoglobin is easily estimated, since 1.34 c. c. of O_2 equals 1 gram hemoglobin.

For a full description of the details of the method the article by Haldane and

Barcroft, or the account given in Brugsch and Schittenhelm's "Special Methods," 1914, pages 36-43, should be consulted.

(ii) The Carbon-monoxid Capacity Determined Colorimetrically with Plesch's Wedge-Tube Hemoglobinometer [1]

The most convenient method of making this estimation is by the use of Plesch's wedge-tube hemoglobinometer.

In the standard wedge-tube, a glass wedge (much like an agar slant) makes up one part, the base of the wedge at the bottom of the tube; this leaves a wedge-shaped space (base upward) in the other half of the tube, to be filled with the standard solution. This standard solution is made up from blood with a carbon-monoxid capacity of 20 volumes per cent (corresponding to 14.9 g. Hb per 100 c. c. of blood). A 1:200 dilution of such blood is saturated with CO and then hermetically sealed in the wedge-tube with an excess of free CO.

In an adjoining tube is placed the blood to be tested; this is saturated with CO (by mixing with water previously shaken with illuminating gas), and diluted exactly 200 times.

By means of a ratchet, one tube is raised, or lowered, until the colors of the two tubes seen through a slit correspond. One reads off, on a scale, the hemoglobin content, in terms of percentage of the standard blood.

This is a reliable instrument. It has not come into general use, however, as yet. The necessity of using illuminating gas is a nuisance.

In Haldane's hemometer (Jour. Physiol., Camb., xxvi, 501), a similar use is made of CO.

(*h*) *Quantitative Variations in the Hemoglobin Content of the Blood under Normal Conditions*

The marked variations under normal conditions of the hemoglobin value have already been referred to, under the use of Sahli's hemometer. Women, on the average, have a lower hemoglobin value than men, and the variations in each sex may normally be as much as 20 points on the Sahli scale.

People in robust health, and especially people who live in the country, have higher values than people in ordinary health and than city dwellers. In women, there is normally a diminution at the menstrual period.

(*i*) *Quantitative Variations in the Hemoglobin Content of the Blood in Pathological States*

When the hemoglobin value is lower than normal, that is, below 80 for men or 70 for women, on the Sahli scale, the condition is called *oligochro-*

[1] Made by B. B. Cassell, Frankfurt a/M.

memia. As a rule, this is associated with decrease, also, in the number of red corpuscles (*oligocythemia*). When the diminution in hemoglobin-content goes parallel with the decrease in the number of red corpuscles, the color-index (*q. v.*) remains 1; when the hemoglobin content is diminished to a greater extent than the decrease in the number of red cells, as, for example, in chlorosis, the color-index is below 1. In some forms of anemia, especially in the hemolytic anemias (Addison-Biermer type), the diminution of the hemoglobin content is relatively less than the decrease in the red blood-corpuscles; in these cases the color-index is often greater than 1.

A transient oligochromemia occurs in hydremic states. An oligochromemia is present in all the anemias and leukemias, no matter what their cause.

The opposite condition, an increase in the hemoglobin-content, or polychromemia, is seen in the erythrocytoses and in the erythremias (*q. v.*). Usually, in such cases, the color-index is somewhat high.

(*j*) *The Determination of the Color-index* (*C. I.*)

If one has counted the number of red blood-corpuscles in a cubic millimeter of blood, and has estimated the hemoglobin by one of the methods described above, one can then draw conclusions regarding the average hemoglobin-content of the single red corpuscles. This relation of the number of the red cells to the amount of hemoglobin is known as the *color-index* of the red blood-corpuscles. We calculate the color-index (C. I.) according to the following formula, $\text{C. I.} = \frac{\text{Hb found}}{\text{Hb Normal}} \div \frac{\text{R. B. C. found}}{\text{R.B.C. normal.}}$ If one take the average red count, in man, as 5,000,000 to the c. mm., and, similarly, take the minimal normal amount of hemoglobin to be 13.77 grams in 100 c. c. of blood (= 80 Sahli; = 90 Miescher; = 86 Plesch; = 110 Tallqvist), then these relative values correspond to the color-index 1.

The actual calculation will vary with the method of hemoglobin estimation used. If, for example, the Hb-value has been found to be 40 (Sahli) and the red cell count 3,200,000, then the $\text{C. I.} = \frac{40}{80} \div \frac{3{,}200{,}000}{5{,}000{,}000} = 0.78.$

For quick calculation "in my head" I always use the quotient:—hemoglobin-percentage of normal, divided by the red-cell-percentage of normal, getting the latter by multiplying the number of hundreds of thousands of red corpuscles by two; thus, if the red-cell count is 3,200,000,

the red-cell-count percentage is 64. Taking the case above mentioned, the Hb-value (Sahli) was found to be 40; the minimal normal count on the Sahli scale is 80 (in the male); accordingly the hemoglobin percentage of normal is $\frac{40}{80} \times 100 = 50$ per cent. The quotient for getting the color-index is $\frac{\text{Hb percentage}}{\text{R. B. C. percentage}} = \frac{50}{64} = 0.78$.

In calculating the color-index for women, I take 4,500,000 as the normal red count, and Hb-value 70 (Sahli) as the minimal normal Hb-value.

Obviously, when the amount of hemoglobin is diminished to a greater extent than the number of red corpuscles, the color-index will be smaller than 1, sometimes as low as 0.5 (*low color-index*); and, on the other hand, when the number of red corpuscles is more reduced than the hemoglobin-content, the color-index will be greater than 1, sometimes as high as 1.8 or even 2.1 (*high color-index*).

The color-index is usually low in chlorosis and in all secondary anemias (as in nephritis, in ulcus ventriculi, in uncinariasis, in bilharziosis, in carcinoma, in posthemorrhagic anemias, and in Banti's disease); it is usually high in the chronic hemolytic anemias (Addison-Biermer type, dibothriocephalus anemia, anemia pseudoleukemia, infantum, hemolytic icterus).

When the color-index is pathologically low, the small amount of Hb in the single red corpuscles is easily recognizable under the microscope, in stained, as well as in unstained preparations. Though some of the corpuscles may have a normal, or nearly normal, color, the majority can be seen to be abnormally pale; they show, especially, an exaggerated central pallor at the biconcavity.

When the color-index is abnormally high, as in the Addison-Biermer anemia, the hyperchromemia of the individual red corpuscles is easily recognizable, microscopically, in stained, and in unstained specimens; and, usually, the diameter of a large percentage of the corpuscles (macrocytes) is increased.

To judge, under the microscope, of the color-index, the specimen must be suitable; the blood must not be spread out too thin, or the red corpuscles will be flattened out, and the evidences of biconcavity obliterated. We choose areas in which the biconcavity is visible in all the red corpuscles.

As Naegeli emphasizes, the calculated C. I. is entirely independent of all variations (1) in the total amount of blood, (2) in vasomotor influences, (3) in osmotic conditions and (4) in other factors that dilute, or concentrate, the blood. Thus, to illustrate by a single example, a swelling of the red corpuscles cannot affect the C. I. in any way.

A high color-index is by no means always, though it is frequently, associated with the presence of macrocytes in the blood.

As will be seen in the section on Special Diagnosis of Diseases of the Blood,

we make much use of the color-index in the differential diagnosis of the different forms of anemia.

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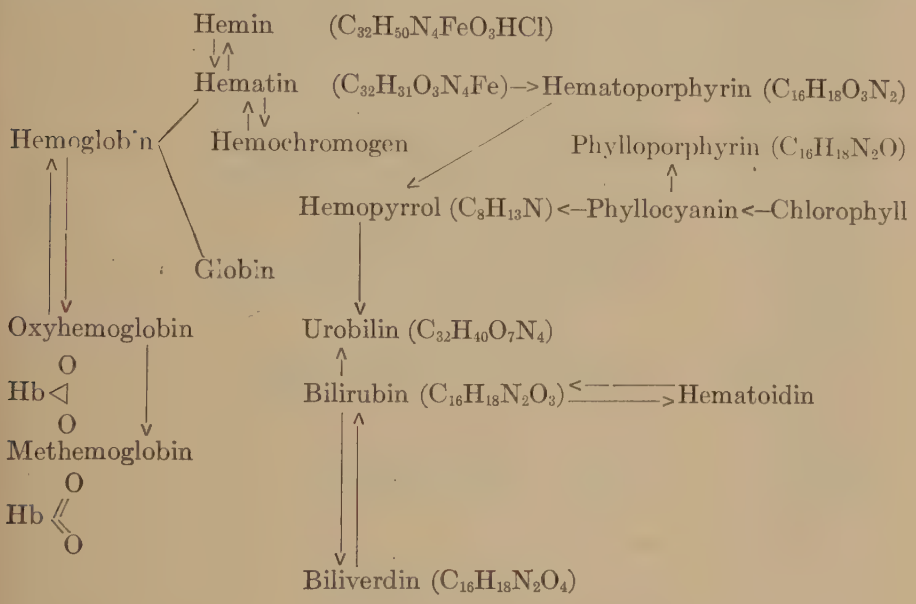
3. Methods for Detecting Qualitative Disturbances of the Hemoglobin Content of the Blood (Spectral Analysis)

The hemoglobin of the arterial blood is oxyhemoglobin. In the venous blood, there is some oxyhemoglobin, and, also, some reduced hemoglobin. Under pathological conditions, in addition to these two normal forms of hemoglobin, we may at times find, (1) methemoglobin, (2) carbon-monoxid

hemoglobin, or (3) sulphemoglobin. In certain conditions, either inside or outside the blood, we may find decomposition products of hemoglobin, including, (1) hematin, (2) hematoporphyrin, (3) hematoidin, identical with bilirubin, (4) hemosiderin, and (5) malarial pigment, possibly identical with hematin.

The relations between hemoglobin (reduced hemoglobin) and (1) other forms of hemoglobin and (2) various derivatives of hemoglobin, are well shown in the accompanying table, taken from Ralph Webster's excellent text-book.



The best method of recognizing these different forms of pigment is by spectroscopic analysis.

For clinical purposes, the ordinary hand spectroscope, especially the form in which the normal spectrum of sunlight can be directly compared with the spectrum of the fluid under examination, is all that is necessary.

The solution is placed in a test tube, or, better, in a small glass receptacle with parallel sides. Blood, itself, should be diluted with from 10 to 100 parts of water before spectroscopic examination.

The spectroscopic characters of the different pigments are as follows:—

(a) **Reduced Hemoglobin.**—There is one broad band between D and E.

(b) **Oxyhemoglobin.**—There are two absorption bands, one in the yellow, narrower, darker and sharper, lying on the line D; the other in the green, broader, less definite, and less dark, lying on the line E. In concentrated solutions, the bands become broader, so that they approach

one another. In very dilute solutions, the broader band disappears first. On adding ammonium-sulphid solution, the oxyhemoglobin is converted into reduced hemoglobin, and its broad band between D and E appears.

Fig. 295.—Pocket Spectroscope—Fitted with a Mirror Adjustment so that One Gets Two Spectra with the Same Light Rays. The One Spectrum Serves as a Scale, the Other for the Observation of the Absorption Bands. (After Vogel, from C. Neuberg, "Der Harn, etc.," published by J. Springer, Berlin.)

(c) **Methemoglobin.**—In alkaline solution, there is a narrow absorption band in the yellow at D, and one in the yellowish-green and the green; in acid and in neutral solutions, there is an absorption band in the yellow at D, one in the greenish-yellow near E, and a broader one in the green, between b and F. On the addition of ammonium sulphid, we get, first, the spectrum of oxyhemoglobin, and, later, that of reduced hemoglobin. To the naked eye, a serum containing methemoglobin can be recognized by its brownish color.

(d) **Carbon-Monoxid Hemoglobin.**—The absorption bands are similar to those of oxyhemoglobin, but the two bands lie a little more toward the violet end of the spectrum, further from D, and, moreover, on addition of ammonium sulphid, no reduction takes place, thus sharply distinguishing CO-hemoglobin from oxyhemoglobin. The blood, to the naked eye, has a cherry-red color, which is very striking.

(e) **Sulphemoglobin.**—There are three absorption bands, two similar to those of oxyhemoglobin, between D and E, and a third in the orange, but not so close to the line C as is the first band of methemoglobin in acid solution. This third band does not disappear on the addition of dilute ammonium sulphid, though the similar band due to methemoglobin does disappear.

Sulphemoglobin is due to H_2S poisoning, often from intestinal abnormalities (Bergh, Clarke); the condition known as "idiopathic enterogenous cyanosis," accompanied by headache and severe constipation, is accompanied by sulphemoglobinemia.

(f) **Hematin.**—In acid and in neutral solutions, there are four absorption bands, one between C and D, and three feebler ones between D and E; in alkaline solution, there is one absorption band to the left of D, and a general darkening of the violet end of the spectrum. On adding ammonium sulphid, we get reduced hematin (hemochromogen),

which makes the band at D disappear, and, in its place, two absorption bands appear, one mid-way between D and E, and the other on the line E.

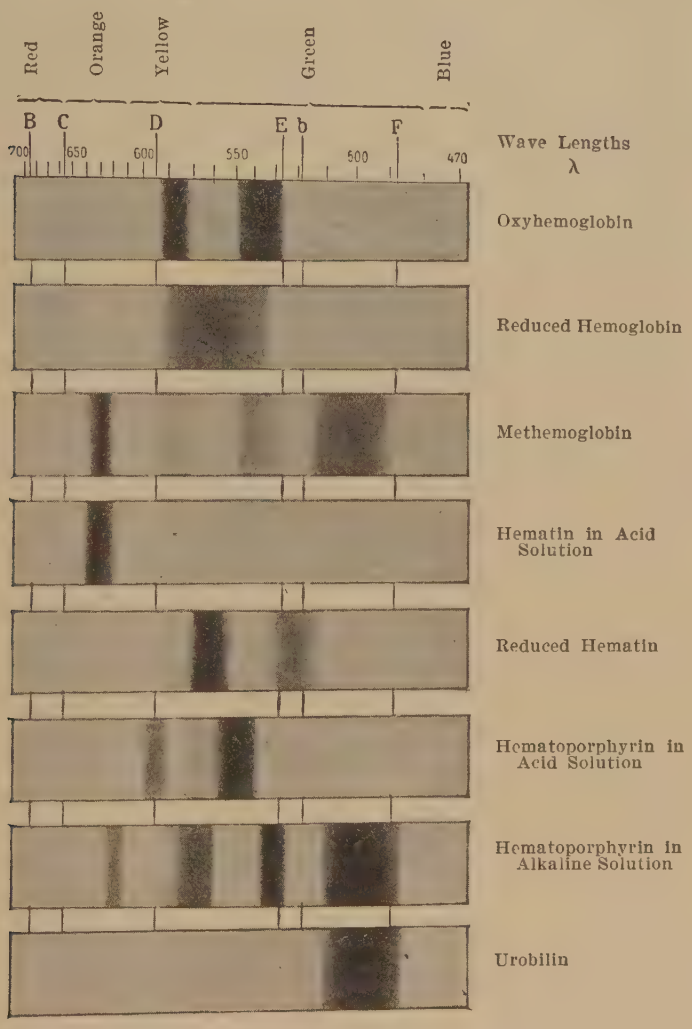


Fig. 296.—The Most Important Clinical Spectra. (After Seifert and Müller, "Diagnostik," published by J. F. Bergmann, Wiesbaden.)

With HCl, hematin forms a characteristic compound, crystallizing with one molecule of the acid to form hemin. As *Teichmann's crystals,* hemin or hydrochlorate of hematin can be prepared from blood stains, important in medico-legal work.

(g) **Hematoporphyrin.**—In acid solution, there are two absorption

bands: one is faint and rather narrow, close to D, between C and D; and the other, darker, occupies a broad area between D and E. In alkaline solution, there are four absorption bands, a most characteristic spectrum; one narrow band lies between C and D; then comes a broader band, beginning at D, and extending half-way to E; a third band lies close to E, between D and E; and the fourth, broadest, darkest band, occupies most of the interval between b and F, going a little beyond the F line. Hematoporphyrin is an important derivative of hemoglobin. It is further discussed under hematoporphyrinuria (*q. v.*).

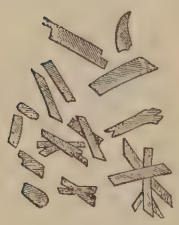


Fig. 297. — Hemin Crystals. (After Bizozero, in H. Sahli, "Klinischen Untersuchungs-Methoden," published by F. Deuticke, Leipzig.)

(h) **Malarial Pigment.**—In alkaline alcoholic solution, malarial pigment yields a single broad absorption band, starting sharply at D and extending to the left, gradually growing feebler in the orange between C and D.

This pigment is probably identical with hematin (Brown), though it was formerly supposed to be one of the melanins. The melanins, however, are quite distinct from malarial pigment; they yield different reactions with decolorizing agents and with solvents.

The pathological conditions in which abnormal forms of hemoglobin appear are numerous. They consist chiefly of intoxications.

Thus, in poisoning by carbon monoxid, by nitrous oxid, by hydrogen sulphid, or by prussic acid, we may get carbon-monoxid hemoglobin, sulphemoglobin, or cyanmethemoglobin, owing to the fact that these gases have a greater affinity for the hemoglobin than has oxygen itself.

In carbon-monoxid poisoning there is often polyglobulia; the eosinophils may completely disappear from the blood.

Methemoglobinemia occurs in association with a number of intoxications that cause hemolysis. Thus, anilin, the phenols, pyrogallol, the nitrites, iodin, and chlorate of potash, are all capable of causing hemolysis and methemoglobinemia. I have often produced methemoglobinemia and methemoglobinuria in rabbits, by injecting, into the ear-vein, human serum, derived from cases of lobar pneumonia. In paroxysmal hemoglobinuria, methemoglobin appears both in the blood and in the urine.

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4. Counting the Formed Elements of the Blood

Hemocytometers.—In order accurately to count the formed elements, the blood must be diluted, and a special instrument, the blood counter, or hemocytometer, has to be employed.

It is best to count the red and white cells separately, since, in counting the white cells, the work is facilitated by destroying the red cells, and, moreover, the blood should be diluted less for counting the white cells, than for counting the red cells.

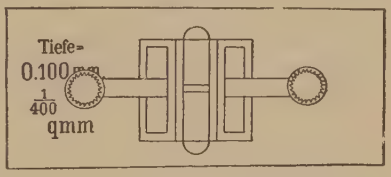

Fig. 298.—Bürker's Counting-Chamber. (After P. Krause, "Lehrb. d. klin. Diagnostik d. inn. Krankh.," published by G. Fischer, Jena.)

For making the dilutions, special mixing pipets (Malassez) have been devised; and for the actual counting, several types of counting-chambers (Thoma-Zeiss, Breuer, Bürker), with a variety of rulings (Thoma, Zappert, Elzholz, Ewing, Türk, Neubauer) are available.

(*a*) *Enumeration of the Red Blood-Corpuscles* (*R. B. C.*)

The Bürker Counting-Chamber with Neubauer's Ruling.—The enumeration of the red corpuscles is best made with a Bürker modification of the Thoma-Zeiss counting-chamber (made by Zeiss), and, by preference, with the form having the Neubauer ruling, shown in Fig. 299. This ruling offers many advantages over the original Thoma design and should be more generally used.[1] The ruled area is divided into nine large squares, each large square measuring 1 mm. on each side; the central square is the one used for counting the red corpuscles, and it is subdivided into 400

[1] [The original Thoma-Zeiss counter should no longer be purchased, as the Bürker chamber, with Neubauer ruling, is far superior.]

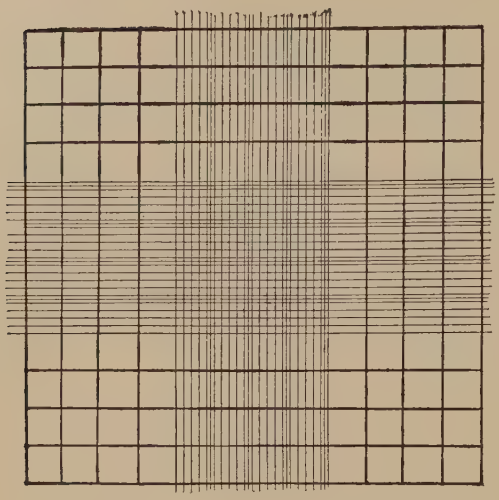

Fig. 299.—The Neubauer Ruling of the Hemocytometer. (From R. S. Morris.)

small squares, each of them 1/20 mm. on a side, enclosing an area of 1/400 sq. mm. These smallest squares are, by means of double lines, grouped into sixteen intermediate-sized squares, each of the latter containing a block of twenty-five small squares.

The Diluting Pipet.—The dilution of the blood is made in a mixing pipet especially devised for the purpose. (Fig. 300.) This mixing pipet consists of a calibrated glass capillary tube that leads to an ampulla, into which the blood is sucked up and within which it is diluted; in the ampulla lies a small glass pearl, which insures thorough mixing of the blood with the diluting fluid, on shaking. Blood is sucked up (without air bubbles) from a freshly drawn drop (see Method of Securing Blood for Examination), as quickly as possible, until it reaches the mark 0.5 on the capillary tube. Care should be taken not to draw blood above the mark; if it should rise very slightly above it, its level may be lowered by drawing the finger, cautiously, over the tip of the pipet. The end of the pipet is then wiped off without disturbing the level of the blood inside and is then introduced into the diluting fluid, which is drawn in until the mark 101 is reached. While drawing in the diluting fluid, the pipet is gently revolved so that the glass pearl in the mixing chamber rolls about, thus beginning the mixing immediately and preventing the retention of air bubbles adjacent to the pearl. The blood thus undergoes a dilution of 1 : 200. (In very marked anemia, it is better to use a dilution of 1 : 100, the blood being drawn up to the mark 1.) At the moment the contents of the pipet reach the mark 101, the suction is stopped and the end of the tube is closed with the tip of the tongue. The pipet is then closed, below, with the middle finger, and the thumb occludes the other end. The pipet is then held horizontally and carefully shaken, for from 2 to 5 minutes.

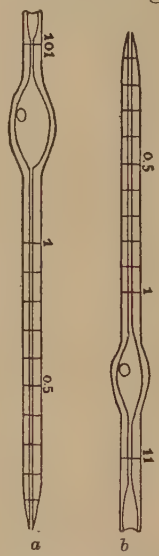

Fig. 300.—Pipets for Red and White Blood-Corpuscles. (a) Red-Corpuscle Pipet; (b) White-Cell Pipet. (After P. Krause, "Lehrb. d. klin. Diagnostik d. Inn. Krankh.," published by G. Fischer, Jena.)

The Diluting Fluid.—As a diluting fluid, one may use a 0.9% solution of NaCl, or, preferably, Hayem's solution, which has the following composition:—

Bichlorid of mercury	0.5
Sodium sulphite	5.0
Sodium chlorid	1.0
Water (distilled)	200.0

Placing the Diluted Blood in the Counting-Chamber.—After the blood and the diluent have been carefully mixed with the pipet in the horizontal position, several drops are blown out, or sucked out by filter-paper, from the pipet, in order to get rid of all the fluid in the capillary tube that has not undergone admixture with the blood.

The diluted blood is now ready for the counting-chamber. A special polished cover-glass has previously been placed over the Bürker counting-chamber (in such a manner that Newton's colored rings are clearly visible), and fixed in position. The two semi-circular projections, at the anterior and posterior edge of the slide, are, each, now quickly touched with the tip of the pipet, whereupon the diluted blood flows, by capillary attraction, under the cover-glass and over the ruled areas to be counted in the counting-chamber. By this method, a more uniform distribution of the corpuscles is possible than with the older forms of blood counters, and, moreover, since the chamber has two ruled areas, separated from each other by a moat, or gutter (at least 2 mm. wide), two different preparations for counting are made at one and the same time. If desired, one side of the Bürker chamber may be filled with blood diluted for a red-corpuscle count, the other side with a different dilution of blood for the white-cell count.

Counting the Red Corpuscles.—After waiting at least three minutes, until the corpuscles have settled to the bottom of the chamber, one glances at the entire preparation, first with a low power of the microscope, to make sure of an even distribution of the corpuscles; if the distribution be not even, another preparation should be made.

The counting can next be begun with the aid of a fairly high power (say Leitz Oc. 1, Obj. 6). We count all the cells in the four corner blocks of squares in the finely ruled area, that is, a total of 100 small squares in each of the two ruled areas of the Bürker chamber, or a total, in the two ruled areas, of 200 small squares (C. P. Emerson). The rule is followed that all corpuscles touching the line on two adjacent sides of a small square are included in the count, but those touching the line of the other two sides are not included in the count, of that square.

Calculating the Number per Cubic Millimeter.—The final calculation is made as follows: Since the depth of the layer of blood between the cover-slip and the bottom of the chamber is 0.1 mm., and since each of the smallest squares measures 1/20 mm. on each side, the cubic capacity of each square = 1/10 x 1/20 x 1/20 = 1/4000 c.mm. If the cells in 200 such squares have been counted, the total cubic area of 200/4000, or 1/20 c.mm. of diluted blood has been gone over. As the dilution used was 1:200, to calculate the number of cells in one cubic millimeter of undiluted blood, the total number counted in 200 small squares (1/20 c.mm.) must be multiplied by 200 x 20, that is by 4000; if only 100 small squares were counted, the multiplying factor would of course be 8000.

Care of the Hemocytometer.—Immediately after finishing a count, the counting-chamber and cover-slip should be rinsed with distilled water and dried with a piece of clean linen; no fluid other than water should be used for the chamber, since alcohol or ether may dissolve the cement.

Pipets are cleansed by passing through them successively, (1) distilled water, (2) alcohol, (3) ether, and (4) dry air. Blood should not be allowed to stand long in either the counting-chamber or the pipet. Should a clot form in the capillary tube, it can usually be removed by a stiff horse-hair (never by a wire); if the diluting chamber grows dirty it can be cleaned by drawing in HNO_3 and immersion of the whole pipet therein, after removal of the rubber tubing.

The Thoma-Metz Hemocytometer.—This very simple instrument has recently been introduced by Leitz. There is no ruling on the slide; the ruling is in the eye-piece.

The ordinary dilution 1:100 is made; the chamber is said to be such that when the corpuscles in the large square are counted, and five ciphers are appended to the number counted, the number of red corpuscles in a cubic millimeter of blood is obtained. Thus, if there are forty-eight red cells in the square, the red count is 4,800,000.

Fig. 301.—The Thoma-Metz Hemocytometer. The Ruling is in the Eye-piece, not on the Slide. (By courtesy of E. Leitz, N. Y.)

For making a count of the white corpuscles, a 1:10 dilution of blood is used; to the number of white cells found in a large circle, three ciphers are appended, and the result is the number of white cells per cubic millimeter. Thus if the circle contain 8 white cells, the count is 8000. I have had no experience with this instrument and do not know how accurate it is.

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i. Variations in the Number of Red Corpuscles Under Normal Conditions

While we take, arbitrarily, as the normal number of red blood-corpuscles per c. mm., 5,000,000 for men, and 4,500,000 for women, still, as we have seen in the hemoglobin determinations, there are very marked variations within the limits of normal. In man, counts between 4,000,000 and 5,500,000 are within normal limits; in women, counts between 4,000,000 and 5,000,000 cannot be considered abnormal.

In new-born babies, the count is high, but, after birth, it gradually falls to normal. After the suckling period, small children have, on the average, a lower count than children over ten years of age. In old people, the count tends to be somewhat lower than at the prime of life.

There is a slight reduction in the count at each menstrual period in women. During pregnancy, the count is variable; it may be either increased, or diminished.

At high altitudes, the number of red cells increases, though the number soon becomes normal on return to the sea level. Recently, these changes due to altitude have been disputed.

Formerly, climate, too, was supposed to have a marked effect upon the red count, and we heard much of polar anemias and tropical anemias. Though anemia may occur in polar regions and in the tropics, what has been described as such has often been, apparently, a pseudo-anemia (*q. v.*) and not a diminution in the red count per c. mm. On fasting, and on reduction of the water-intake, there may be a concentration of the blood, with increase of the R.B.C. count. The effects of vasomotor influences upon the red count and upon the hemoglobin content of the blood, have already been referred to. These physiological variations, due to sex, age, altitude, nutrition, exercise, etc., should be kept in mind when judging of the significance of a given blood count.

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ii. Variations in the Number of Red Corpuscles Under Pathological Conditions

A diminution of the red count (*oligocythemia*) is met with in the various anemic states. The count may be far below 5,000,000 per c. mm. The oligocythemias are due either (1) to loss of red blood-cells, or to increased destruction of red blood-cells, on the one hand, or (2) to insufficient blood formation, on the other.

An increase in the number of red blood-cells (*polycythemia; hyperglobulia*) is met with (1) in all conditions that cause a concentration of the blood, (2) in conditions associated with venous stasis, and, also, (3) as an especial disease, in which there is increased formation of blood (hypererythropoiesis).

(*b*) *Enumeration of the White Blood-Cells* (*W. B. C.*)

For this purpose, the same Bürker counting-chamber is used, but a special mixing pipet, other than that used for R.B.C., is employed. The "white" pipet provides for either a 1 : 10 or a 1 : 20 dilution of the blood. As a diluting fluid, none is more satisfactory than Türk's, which has the following composition[1]:—

Glacial acetic acid	3.0
1 per cent aqueous solution of gentian violet	3.0
Distilled water	300.0

This fluid lakes the red corpuscles, rendering them invisible, and at the same time stains the nuclei of the white cells, thus making them very easily recognizable. Some workers omit the gentian violet, as the acetic acid, alone, makes the nuclei stand out prominently.

Blood is slowly drawn in, up to the 0.5 mark on the pipet, after which the diluting fluid is sucked in until the mark 11 is reached, the

[1] The fluid should be freshly prepared, or the growth of yeast cells in it may lead to confusion.

pipet being at the same time rotated and jarred, in order to prevent any air-bubble from remaining on the glass pearl; the resultant dilution is 1 : 20. The pipet, held horizontally, is shaken for from 2-3 minutes, to ensure thorough admixture. Having filled the counting-chamber in the same way, and observed the same precautions as when making a count of the red corpuscles (*q. v.*), and having waited at least three minutes for the cells to settle upon the floor of the chamber, the white cells in the four large coarsely-ruled corner squares (each square is subdivided into 16 smaller ones for ease in counting), and in the central finely-ruled square of 400 smaller units, are counted in each of two preparations, that is, 10 large squares in all. Since each large square measures 1 mm. on a side, and the chamber is 0.1 mm. deep, the cubic content of each of these large squares is 1/10 c. mm. Hence if 10 of these large squares be counted, it is only necessary to multiply the number of cells by the dilution to ascertain the number of white cells in one cubic millimeter of blood.

Nucleated red cells are counted as white blood-cells, and the number deducted after the differential count has been made in blood smears prepared from blood taken at the same time.

The number of the white corpuscles varies in health from 7,000-10,000, with the great majority of all normal counts averaging around 8,000. In making any leukocyte count, a great many factors that influence these cells must be carefully considered. Galambos, for example, has shown that, in the same person, on the same day, the total white count may show variations of nearly 100 per cent. While this is doubtless unusual, it is certain that vasomotor influences, age, digestion, altitude, local changes in the circulation, etc., all modify the white count to a certain degree, and hence must be reckoned with.

When the number of white blood-corpuscles is pathologically diminished (below 7,000 per c. mm.) the condition is spoken of as a *leukopenia;* when the white cells are increased in number (over 10,000 per c. mm.) *leukocytosis* is said to exist. In such cases, it is very important, not only to determine the *absolute number of white cells present,* but, also, to ascertain the relative percentages of the different types of white cells in the blood by means of a differential count on stained preparations (*q. v.*).

According to the variety of leukocyte that is increased, we can subdivide the leukocytoses into (1) neutrophilic leukocytoses, (2) eosinophilic leukocytoses, (3) basophilic leukocytoses or mast-cell leukocytoses, (4) lymphocytoses, (5) large mononuclear leukocytoses, and (6) myelocytoses. As a rule, however, the term leukocytosis is reserved for increases in the neutrophilic, eosinophilic and basophilic polymorphonuclear leukocytes, and the term lymphocytosis for an increase in the lymphocytes, whereas when myelocytes, myeloblasts or lymphoblasts appear in the blood, we speak of a "leukemic blood-picture," rather than of a leukocytosis. A few myelocytes may occur in the blood with an ordinary neutrophilic

leukocytosis, but one never has much difficulty in distinguishing between such a leukocytosis and the blood of a leukemia.

i. Variations in the White-Cell Count Under Normal Conditions (The Physiological Leukocytoses)

Among the physiological leukocytoses may be mentioned, (1) the leukocytosis of digestion, (2) the leukocytosis of pregnancy, (3) the leukocytosis of the new-born, (4) the leukocytosis after exercise, after over-heating, and after cold baths.

Leukocytosis of Digestion.—There is much difference of opinion, in the bibliography, on this subject. Though the literature is large, there is no unanimity of opinion. Undoubtedly some variations do occur after the eating of food, but there is no constancy. The number of cells may vary between 7,000 and 10,000. Sometimes the polymorphonuclear leukocytes seem to be increased, sometimes the lymphocytes.

Leukocytosis of Pregnancy.—Here, again, there are marked differences of opinion among clinical workers, some holding that a leukocytosis is constantly present in pregnancy, others that it is present only in primiparae, and still others, though they admit a high normal count, denying the existence of an actual leukocytosis in pregnancy. Many of the earlier views were based upon counts made at a time when the daily variations in the white cell count were not known, and also at a time when too small counting chambers, such as the old Thoma-Zeiss, were used, with consequently unreliable results. The more recent studies are in agreement and indicate that no noteworthy leukocytosis exists in pregnancy, though the count reaches the upper limit of normal, especially in primiparae. The slight increase is due to polymorphonuclear neutrophils.

During labor, an actual neutrophilic leukocytosis, 20,000 and more, sometimes occurs. It is partly a posthemorrhagic phenomenon, partly due to local injury, with inflammation. Under normal conditions, it soon passes.

In the puerperium, there is a gradual restoration of the normal number, though the count continues rather high during the period of the lochia. If any infection occurs, the count quickly runs up.

Leucocytosis of the New-born.—In new-born babies, the white count averages from 17,000 to 19,000; the minimal count varies between 7,600 and 11,900; the maximal count recorded is 32,500.

The number of white cells decreases within a few days after birth. According to Takasu, the average for the first four days of life is around 18,000, for the 5th to the 11th day around 14,370. This leukocytosis is due to an increase in the polymorphonuclear neutrophils, but its origin is obscure. Many factors are probably responsible (mechanical effects of birth, altered nutrition, environmental influences).

Leukocytosis After Exercise and After Over-heating.—After violent *exercise* there is marked increase in the white-cell count (myogenic leukocytosis of Grawitz). Thus, after rowing for half an hour, Wagner and Rosenthal found that the white cells increased from 4,400 to 11,200 in one instance, and from 7,500 to 11,700 in another. Differential counts showed, at first, an increase of the lymphocytes, with only a slight increase in the neutrophils. Later, the lymphocytes decreased and the neutrophils increased in number (Rosenthal). Whether or not the stimulus to the leukopoietic apparatus is really myogenic in origin is not known.

After *over-heating,* a rapid increase in the leukocytes has been observed, both in experimental animals, and in man. Vasomotor influences upon the cutaneous vessels are probably of importance here, as indicated by the leukocytoses occurring after both warm and cold baths (Thayer, Rovighi, Winternitz).

Recently, very careful studies of the effect of thermal stimuli have been made by E. Becker, who examined not only the blood from the finger, but also blood from the median vein. He found that, after cold douches and cold baths, the red blood corpuscles, in both the capillaries and the veins, undergo an even increase in number, but that, on the contrary, the leukocytes in the capillaries at first show a considerable increase, but there is a decreased number in the veins. All these changes had disappeared after an hour or two. Becker concluded that the effect of cold is to retain the leukocytes in the capillaries, through adhesion to their margins. Further studies in this field are, as Naegeli emphasizes, desirable, and the blood count should be controlled by other methods of examination (viscosimetry). Enough work, however, has been done to teach us to beware of confusing apparent leukocytoses due to disturbances in the distribution of the white cells in the blood vessels, with true leukocytoses due to increased leukopoiesis.

ii. Variations in the Number of White Blood-Cells Under Pathological Conditions (The Pathological Leukocytoses and Leukopenias)

The study of the leukocytoses under pathological conditions has turned out to be of great help in clinical diagnosis, especially in the infectious diseases. It has been found that the toxic products of the bacteria often lead to intense reactions on the part of the bone-marrow and of the lymphatic system. Also, in chemical intoxications of various sorts, after hemorrhage, and after inflammation, no matter what the cause, leukocytoses are prone to occur. Though much work remains to be done in clearing up the causation of leukocytosis, several groups seem to be well established on an etiological basis. These include: (1) the leukocytoses of certain infectious diseases, (2) the leukocytoses of intoxications, (3) the leukocytoses associated with hemorrhage, (4) the leukocytoses associated with malignant neoplasms, and (5) certain other leukocytoses. Formerly, a leukocytosis due to cachexia was described, and also an agonal leukocytosis, but these conceptions have been given up.

(1) *The Neutrophilic Leukocytoses*

(a) **The Leukocytoses of Certain Infectious Diseases.**—The leukocytosis in these diseases is doubtless due to the stimulating effect of the toxins upon the leukopoietic tissue of the bone-marrow, especially in the cases in which neutrophilic leukocytosis is seen. If the poisoning be too severe, there may be a leukopenia instead of a leukocytosis; thus, in diseases ordinarily accompanied by a neutrophilic leukocytosis, the occurrence of a leukopenia is of bad omen (*e. g.*, pneumonia, peritonitis).

It is especially in the infections with pyogenic organisms (streptococci, staphylococci, pneumococci, gonococci, meningococci) that polymorphonuclear neutrophilic leukocytoses are met with. This accounts for the

occurrence of such a leukocytosis in sepsis, pneumonia, erysipelas, meningitis, tonsillitis, arthritis, endocarditis, appendicitis, etc. Two factors have to be considered in the origin of such leukocytoses: (1) the chemotactic effect of the bacterial products, attracting leukocytes into the blood, and (2) the stimulating effects upon the leukopoiesis in the bone-marrow.

There is a group of infectious diseases, including typhoid fever and measles, in which, instead of a leukocytosis, there is a leukopenia. We must assume that, in these diseases, the toxic substances produced paralyze the leukopoietic function of the bone-marrow.

Naegeli has subdivided the infectious diseases into three groups, as follows:

Infectious Diseases Associated with Leukocytosis.—The pneumonias; sepsis with local suppurations, as long as they are active and progressive (appendicitis, abscesses, purulent peritonitis, empyema); scarlatina; erysipelas; epidemic cerebrospinal meningitis (and other forms of suppurative meningitis, though rarely in the tuberculous form); cholera; smallpox; chicken-pox; whooping-cough; diphtheria; acute muscular rheumatism; beriberi; acute polyneuritis; acute encephalitis; acute syphilis.

Infectious Diseases Not Associated with Leukocytosis.—Typhoid fever; measles; German measles; mumps; influenza; tuberculosis (when uncomplicated); glanders; acute poliomyelitis.

The occurrence of leukocytosis in one of these diseases usually indicates a complication of some sort, especially a complicating infection with some pyogenic organism.

Infectious Diseases Associated with Temporary Leukocytosis.—Sometimes, in malaria, a leukocytosis is seen at the time of the chill, but, as a rule, in this disease there is leukopenia.

The main features of the blood picture can be seen by consultation of the table on page 61.

(b) **The Leukocytoses in Intoxications** (*Toxic Leukocytoses*).—Aside from the toxic effects of infections described above, leukocytosis may be due to other chemical substances; thus, organ extracts, especially those rich in nucleins, when injected, give rise to leukocytosis. Certain drugs (antipyrin, antifebrin, phenacetin, camphor, collargol, digitalis preparations) can cause a leukocytosis. Hemolytic poisons, like potassium chlorate, pyrodin and pyrogallol, can cause leukocytosis.

(c) **The Leukocytoses in Hemorrhage** (*Posthemorrhagic Leukocytoses*).—The white-cell count is increased soon after the occurrence of a hemorrhage, the number of white cells corresponding, more or less closely, with the number of young erythrocytes and normoblasts appearing in the blood. Such a posthemorrhagic leukocytosis passes off in a few days. The increase in white cells is due, chiefly, to polymorphonuclear neutrophils, but an occasional myelocyte may be seen. There can be no doubt that the leukocytosis, here, is due to an increase in the activity of blood formation in the bone-marrow, and is probably coincident with a conversion of some of the fatty marrow into functional red marrow (compensatory hypertrophy of the hemopoietic organs).

BLOOD PICTURE IN INFECTIOUS DISEASES

(After Seifert and Müller.)

Disease	Total White Count	Eosinophiles	Lymphocytes	Remarks
Typhoid and Paratyphoid	Decreased	Absent	Rel. increased	Blood platelets decreased
Typhus exanthematicus	Increased	.....	.....	.....
Scarlet Fever	Increased	Increased	.....	In severe cases, often punctate erythrocytes
Measles	Decreased	Decreased or O.	Rel. decreased	During the incubation, leukocytosis
Roseola	Decreased	Normal	Rel. increased	Many transitionals
Variola	Increased	Appear	Increased	Many large lymphocytes and transitionals
Diphtheria	Increased	Decreased	.....	Myelocytes in children frequently; after the serum injection in children, often eosinophilia
Angina	Increased	Normal or dec.	.....	.....
Erysipelas	Increased	Absent	.....	.....
Polyarthritis rheumatica	Increased moderately	Appear; later increased	.....	Often anemia in convalescence
Sepsis	Increased (exceptionally decreased)	Absent	Rel. decreased	In the later stages, always anemia (at the end diffuse and punctate basophilia with nuclear particles)
Miliary Tuberculosis	Normal or decreased	Absent	.....	.....
Influenza	Normal or decreased	Appear; in severe cases decreased or O.	.....	.....
Pneumonia	Increased	Decreased or O.	.....	Blood platelets decreased during the crisis; further rise in leukocytes after the crisis with empyema
Pertussis	Increased	.....	Rel. increased	.....
Meningitis epidemica	Increased	Decreased or O.	.....	Fibrin increased
Meningitis tuberculosa	Normal or mod. inc.	Appear	.....	Fibrin decreased
Parotitis epidemica	Increased	.....	Increased	.....
Impetigo contagiosa	Increased	Increased	.....	.....
Plague	Moderately increased	.....	.....	.....
Cholera	Increased	.....	.....	Marked leukocytosis gives unfavorable prognosis; the erythrocytes in stadium algid. often increased
Malaria	May be increased at beginning at the height of the fever often, in Estivo-autumnal, decreased	At the beginning decreased, otherwise normal	Decreased during the fever, after the fever increased	Not infrequently leukopenia during the whole course
Recurrent Fever	Decreased	.....	Rel. increased	Secondary anemia
Trichinosis	Increased	Increased	.....	.....

(d) **Leukocytoses Associated with Malignant Neoplasms.**—In carcinoma and sarcoma, it is not uncommon to meet with polymorphonuclear leukocytoses of considerable grade, but this is not a constant finding, and it would appear that such a leukocytosis is due, not so much to the carcinoma, or sarcoma, *per se,* as to necrotic changes in these growths, or to inflammatory changes in their neighborhood. Should a carcinoma, or a sarcoma, metastasize into the bone-marrow, then a high grade of leukocytosis may develop, owing to the irritation of the marrow; the white-cell count may rise as high as 50,000 (Naegeli). Most of the new cells are polymorphonuclear neutrophils, but there is an unusually large number of myelocytes in the blood in such bone-marrow metastases, and their presence is helpful in determining the nature of the leukocytosis.

(2) *The Eosinophilic Leukocytoses*

These are of help in the diagnosis of worm invasions (trichinella, uncinaria, bothriocephalus, echinococcus), of skin diseases (especially pemphigus, arsenical exanthems, and scarlet fever), and of bronchial asthma. They occasionally occur in neurasthenic states, in attacks of mucous colitis, and after the injection of antitoxic sera. In trichinosis, as T. R. Brown first pointed out, the eosinophils may make up more than 50 per cent of all the white corpuscles.

The eosinophilic cells are often markedly increased in myeloid leukemia.

In polymorphonuclear leukocytoses, the eosinophils may be not only relatively, but also absolutely, decreased in number; in the latter case the prognosis is more unfavorable.

Scarlet fever is the only acute infectious disease of presumably bacterial origin, in which, at the height of the disease, a very marked eosinophilia may occur. The number of eosinophils per cubic millimeter may be as many as from 500 to 3000 (Naegeli); this eosinophilia has suggested a cause other than bacterial for scarlatina.

The eosinophilia that occurs in the convalescence from infectious diseases is not fully understood. As is well known, the eosinophils, in severe infections, are often diminished in number, but during convalescence, for example, after typhoid, an outspoken eosinophilia (1200-1500 eosinophils to the cubic millimeter) may appear. In the serum disease, eosinophilia may also be outspoken.

In Hodgkin's disease, we sometimes meet with a high grade of eosinophilia. I have recently seen a case of this disease in which over 60 per cent of the white cells were eosinophils. Eosinophilia may also occur in connection with true neoplasms (sarcoma, carcinoma).

The eosinophils are diminished in number, or disappear entirely, at the onset of most acute infectious diseases (typhoid, pneumonia), in

various intoxications, for a short time after major operations, and in the severer forms of hemolytic anemia.

(3) *The Basophilic Leukocytoses*

An increase of the mast-cells in the blood is met with in certain anemias, in skin diseases (especially urticaria), and, often, in cirrhosis of the liver. The greatest increase of mast-cells met with clinically is that accompanying myeloid leukemia.

(4) *The Lymphocytoses*

An increase in the number of the lymphocytes is known as a lymphocytosis. A relative increase is met with in those infectious diseases that run their course without neutrophilic leukocytosis (typhoid, malaria, whooping-cough), and in the convalescence from certain intoxications. Besides such post-infectious, and posttoxic lymphocytoses, the lymphocytoses of Basedow's disease, and of persistent thymus, should be mentioned. The greatest increase in the number of lymphocytes is met with in the so-called lymphatic leukemias (leukemic lymphadenosis). In the aleukemic lymphadenoses, there may be a relative lymphocytosis.

A diminution in the number of lymphocytes is met with at the beginning of most acute infections. This diminution is both relative and absolute. A very marked diminution late in the course of an infection is of bad omen.

In diseases leading to extensive destruction of lymphadenoid tissue (tuberculosis of the lymph glands, Hodgkin's disease, lymphosarcoma, carcinoma metastases), there may also be a decrease in the number of lymphocytes.

For a description of the relation of the lymphocytes to the growth of tumors in animals, the work of Murphy of the Rockefeller Institute should be consulted.

(5) *Variations in the Number of Large Mononuclear and Transitional Forms*

We are very poorly informed as to the significance of increase, or decrease, of the normal large mononuclear elements of the blood. The bibliography contains many references to the subject, but the results are so conflicting as almost to defy helpful analysis. At present, the most that can be said is that, in tuberculous infections, and in typhoid fever, and after splenectomy, there is often a relative increase in the large mononuclear elements. A relative and absolute increase in the transitional forms is held by Bunting to be one of the characteristics of Hodgkin's disease. (See also Large Mononuclears, and Transitionals, under Stained Blood.)

(6) *The Leukopenias*

A *hypoleukocytosis*, or *leukopenia* is often just as important for diagnosis as its opposite. It may be due to insufficient leukocyte formation, or to the negative chemotactic influence of toxins. Among the diseases in which the absolute number of white corpuscles is decreased in the blood, may be mentioned typhoid fever, malaria, measles, parotitis, glanders, and dengue.

Leukopenia sometimes occurs in very severe infections of the types that, when milder, cause leukocytosis (*e. g.*, pneumonia, sepsis). High grades of leukopenia are also met with in the aplastic anemias and sometimes in severe hemolytic anemias (*q. v.*).

Sudden variations in the number of leukocytes are often helpful in diagnosis; thus a sudden increase during appendicitis may point to abscess formation, or in typhoid, where ordinarily there is leukopenia, to an intestinal hemorrhage, to perforation, to complicating pneumonia or phlebitis.

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(c) *Enumeration of the Blood Platelets (Pl.)*

This may be done either by the older indirect method, or, better, by the direct method of Wright and Kinnicutt.

i. Indirect Method of Enumeration of the Platelets (Sahli)

Sahli uses a 14-per-cent solution of magnesium sulphate, which, though it causes some deformation of the platelets, isolates them well from one another. To this solution, he adds some methyl violet, just enough to leave the fluid, in a 10 c. c. graduate, still transparent. A drop of this violet solution is placed directly upon the cleansed finger-tip. A puncture is made through the droplet by means of a blood-sticker, so that the platelets mix with the preservative fluid the moment the blood flows. A little of the blood is placed upon a counter, or under a cover-slip on an ordinary glass slide, and the relative numbers of platelets and of red blood-corpuscles are determined. Then the red blood-corpuscle count is made, in the ordinary way, and the absolute number of platelets calculated therefrom; thus, if the relation of platelets to erythrocytes has been found to be 1:25, and the red count is found to be 5,000,000, the number of blood platelets per cubic millimeter is $\frac{5{,}000{,}000}{25} = 200{,}000$.

ii. Direct Method of Enumerating the Platelets (Wright and Kinnicutt)

The best method of counting platelets is that introduced by Wright and Kinnicutt. Blood is diluted, in the proportion of 1 : 100 in the ordinary pipet for counting R.B.C., using, as a diluting fluid, a mixture of the following solutions:

Solution A. Brilliant cresyl blue 1:300 (aqueous).

Solution B. Potassium cyanide (C.P.) 1:1400 (aqueous).

These solutions should be quite fresh, or kept in separate bottles, on ice, to prevent the growth of yeasts. They are mixed, and filtered, immediately before use (to avoid precipitates), in the proportion of A:B:: 2:3.

The usual blood-counting chamber is used, with a thin cover glass; Wright and Kinnicutt advise the use of an especially thin cover glass with a central excavation (cover glass No. 146, Zeiss Catalogue), in preference to the ordinary one, though this is not really necessary. It is best to wait for ten or fifteen minutes, after filling the counting chamber, before making the count, in order that the platelets may settle completely on the floor of the chamber.

The various blood elements appear as follows:

(a) R. B. C., as "decolorized shadows."

(b) W. B. C., as well-stained cells, the nuclei dark blue, the protoplasm a lighter blue.

(c) Platelets, as small, sharply outlined, round, oval, or elongated, bodies, stained a shade of lilac; the average diameter is three microns, but this tends to vary inversely with the number present.

One may count the four corner blocks (25 smallest squares in each block) in the Bürker chamber, in each of two preparations, just as in making a red-corpuscle count. The method of calculating the total number per c. mm. is obvious (See Enumeration of R.B.C.).

iii. Variations in the Platelet Count in Health and in Disease

Normally, the blood platelets are said, according to earlier enumerations, to average in number between 150,000 and 250,000 per c. mm. Wright and Kinnicutt, as a result of studies by their method, put the normal number higher (226,000-367,000; average 297,000). The factors causing variations in number, under normal conditions, are not well understood. The platelets have already been described in the general introduction to this section on Diagnosis of Diseases of the Blood, where their origin also is discussed (*q. v.*).

The most constant pathological variations in the number of platelets thus far found have been:

1. A reduced count during the febrile period of acute diseases, and an increased count during convalescence, especially in pneumonia, typhoid and malaria (in this respect behaving like polymorphonuclear eosinophils).
2. An increased count in chronic secondary anemia, in chlorosis, and in myeloid leukemia: a low count, on the contrary, in lymphatic leukemia, and in pernicious anemia as well as in the aplastic stages of any severe anemia.
3. An increased count in chronic diseases, notably in tuberculosis.
4. A reduced count in purpura hemorrhagica.

For a fuller discussion of the behavior of the blood platelets in various pathological states, the article by Duke (1913) may be consulted.

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5. The Microscopic Examination of Fresh Unstained Blood

This is one of the most important methods of examining blood. It should never be omitted, in case an abnormal blood state is suspected. It is essential to have absolutely clean glass slides and covers, preferably such as have not been used before.

(*a*) *The Cleaning of Cover Glasses and Slides*

Two principal methods of cleaning slides and covers are in use; namely, (1) the method of R. S. Morris, and (2) the method of Zettnow.

i. Method of R. S. Morris

(1) Immerse the covers and slides in concentrated sulphuric acid for 24 hours.

(2) Pour off the acid, and wash in running water.

(3) Drain off the water, and cover the glassware with 90-per-cent alcohol for an hour or longer.

(4) Replace the alcohol with chloroform, and dry the glassware as needed. On drying, the cloths used should be absolutely clean and free from fat and from lint. Old linen handkerchiefs are especially useful for the purpose. It is best to leave the glassware in the fluid until it is needed for use. If kept dry, the glass should be placed in a dust-proof receptacle and each slide, or cover-glass, brushed thoroughly with a clean camel's-hair brush before using.

For clinical hematological studies, we use 3/4 inch square cover glasses, No. 2, and 3×1 inch thin glass slides, with straight edges.

ii. Method of Zettnow

[For cleaning slides that have previously been used.]

(1) Dissolve 200 g. potassium bichromate in two liters water with the aid of heat, and stir in, cautiously, 200 c. c. crude H_2SO_4.

(2) Cover glasses that have been mounted in balsam are separated from the slide by warming.

(3) Place the dirty cover-slips in several hundred cubic centimeters of the solution above mentioned, and heat for ten minutes. Any Canada balsam present collects as a greenish mass on the surface and is skimmed off.

(4) Wash the cover glasses thoroughly in cold water, and immerse them for five minutes in dilute NaOH. The procedures 3 and 4 may be repeated if necessary.

(5) Wash in alcohol and dry with soft linen.

(6) Slides are immersed for from two to five days in the potassium-bichromate-sulphuric mixture; they are then washed with water, and wiped with soft linen, moistened in alcohol.

(*b*) *The Fresh Blood Slide*

For quick orientation as to the form and number of red and white cells and platelets present in the blood, and as to the presence, or absence, of parasites and of pigment, it is well to examine a small drop of freshly-drawn blood, spread out in a thin layer between a slide and cover glass, first with the magnification of 300 diameters, and later with an oil immersion lens.

The slide and cover must be *thoroughly* cleaned with alcohol and ether, beforehand. The finger-tip, by preference after a warm hand-bath, or the lobule of the ear, should be cleansed with alcohol and ether, and, after the puncture has been made, blood should flow without any extraneous pressure. The first droplet is wiped off; then a small drop, the size of the head of a small pin is received on the cover glass, and quickly placed upon a perfectly clean slide. If one side of the slide be slightly convex, the drop of blood should be placed on this side. The drop is allowed to spread out on all sides in a thin layer, by capillary attraction, and without any pressure. Some prefer to hold the cover-slip between thumb and forefinger when collecting the blood; others use forceps. In either case, one should act quickly.

The central parts of the thin preparation are usually the best for examination; here the *red corpuscles* will be seen singly, lying flat, beside one another. At the periphery of the fluid, rouleaux may be visible, even in thinner specimens. In such a preparation, only one or two *leukocytes* may be present in one field of the microscope (Leitz Oc. 3, Obj. 1/12). But if more are seen, one should not decide from this, alone, that a *leukocytosis* exists; much depends upon the thickness of the specimen, and upon the distribution of the leukocytes on the slide. A skilled observer can, by looking over different parts of the specimen and estimating the relative number of white and red cells, form a tentative judgment regarding the existence or non-existence of a leukocytosis. But if the red corpuscles be diminished in number, one may easily be deceived; it is much better to rely entirely upon an actual white-cell count made with the hemocytometer. Of course, if an enormous increase in white cells exist, as in *leukemia*, it can be easily recognized in the fresh blood slide.

After familiarizing one's self with the different kinds of white blood-cells as they appear in stained smears (*q. v.*), one can also, after some practice, generally recognize to which group a given white cell in the fresh blood specimen belongs.

The *polymorphonuclear eosinophils* are, of course, easiest recognized by their large, highly refractive granules.

The *polymorphonuclear neutrophils* are also easily distinguished, first, by the extremely numerous, minute, non-glistening, granules in their protoplasm, secondly, by the form of the nucleus, and thirdly, by the fact that cells of this type normally predominate among the white cells.

The *polymorphonuclear basophils*, or *mast-cells*, may be hard to find, as they make up, normally, a very small percentage of the white cells. Should one be seen, it ought to be recognized by its combination of characters: (1) polymorphous nucleus; (2) relatively small size; (3) larger granules than the neutrophil granules, but not highly refractive, thus differing from the eosinophil granules.

A *lymphocyte* is easily recognizable by the facts that (1) it is very small; (2) it consists chiefly of its round or oval non-polymorphous nucleus, surrounded by only a minute amount of protoplasm; and (3) the protoplasm contains no sharply defined granules.

A normal *large mononuclear* white cell can scarcely escape recognition, since (1) it is larger than a P.M.N.; (2) its nucleus is not polymorphous; and (3) it has an abundant protoplasm, which is finely granular. These granulations, however, are not of the same character as those seen in the neutrophils, eosinophils, or basophils.

A *transitional* form, in the fresh, unstained blood, has the characters of a large mononuclear leukocyte, except that it has a distinctly-indented, or a polymorphous, nucleus; it might, unless closely examined, be confused with either a large mononuclear, or a polymorphonuclear neutrophil.

The experienced hematologist will usually be able to recognize an outspoken deviation from the normal proportions of the different varieties of white cells; a marked *lymphocytosis*, or a marked *eosinophilia*, is especially easy to detect; an outspoken *neutrophilia* will also be recognized.

The appearance of large numbers of *myelocytes*, or of *myeloblasts*, could scarcely be overlooked in the fresh blood slide, so that the diagnosis of myeloid leukemia can thus easily be made in outspoken cases.

In the fresh, unstained preparation, the *red blood-corpuscles* are well seen, and should be studied especially as to their *size* and *shape*. Normally, they are equal in size (*isocytosis*); in many anemias, one sees a great variation in size (*anisocytosis*), due to the presence of abnormally large cells (*macrocytes*), and abnormally small cells (*microcytes*). Measurements are best made in stained smears (*q. v.*).

Nucleated red cells (*normoblasts*, or *megaloblasts*) may be visible in the fresh blood, especially if it be drawn during a "blood-crisis" in one of the severe anemias.

Occasionally, fine *ameboid movements* of the red corpuscles are visible. Such ameboid movements in macrocytes and megaloblasts have been especially studied and described by Morris and Thayer.

As the serum evaporates at the edge of the cover glass, it becomes hypertonic, and the corpuscles assume a characteristic crenated appearance. An excellent description of the changes undergone by the red corpuscles during *crenation* (refractile spots, indentations, beadlike spines, shrivelling, asterisk appearance) is given by DaCosta in his book on the blood.

To avoid evaporation and crenation, when it is desired to keep a fresh specimen for longer than a few minutes for study, we seal it, by applying melted vaselin, or melted soft paraffin, along the edge of the cover-slip; this will solidify at once, and the preparation can be kept for several hours without change.

Changes in the external form of the red corpuscles are common in anemia, the cells assuming the shape of a pear, an anvil, a club, or other bizarre forms (*poikilocytosis*). These poikilocytes are best seen in unstained preparations.

In *hydremic states*, the red corpuscles lie strikingly far apart in the fresh blood slide; even in the thicker preparations of fresh blood, the spaces between the rouleaux are larger than normal.

The granular changes, ring bodies, and so-called *degenerative and regenerative forms* of the red cells cannot be well studied in fresh unstained blood; they will be described when we come to the staining of dried and fixed smears.

One must take care not to mistake crenation, and other *artefacts*, for pathological abnormalities of the red corpuscles. If a coverslip or slide be dirty, or moist, the red corpuscles may fragment, or they may swell and hemolyze, or bizarre artificial poikilocytes may develop. The greatest care should be taken to observe a faultless technic in the preparation of the fresh blood slide.

With good technic, one can form, from the fresh blood specimen, a fairly accurate judgment regarding the *Hb-content* of the individual corpuscles, and can prophesy, usually correctly, that a normal, a low, or a high color-index, will be found when the Hb is accurately determined and the red count made.

The *blood platelets* can be recognized in the fresh specimens as minute, non-glistening, greyish or colorless particles, rounded, oval, or multangular in shape, often met with in groups. After the specimen has stood for a time, threads of fibrin begin to appear, radiating out from these groups of platelets.

The Brownian movement of the *hemoconia* ("blood dust") is an interesting feature of the fresh blood slide; the tyro may mistake the hemoconia for parasites!

Among the true *parasites* that may be visible in the fresh blood slide, under pathological conditions, we may mention: (1) malarial parasites; (2) spirilla of relapsing fever; (3) trypanosomes; (4) Leishman-Dono-

van bodies; (5) filaria bancrofti; (6) larvae of trichinella spiralis; (7) anthrax bacilli.

Malarial parasites, when present, can be seen, either within the red cells, or occasionally lying free in the serum. The *ameboid movements* of these parasites, and *flagellation*, can be observed only in such fresh preparations. *Crescents* and *ovoid forms* are especially easy to see in the estivo-autumnal infections, though they are present only in small numbers. Formerly, in Baltimore, we relied entirely on the examination of fresh blood for the diagnosis of malaria. For general diagnostic purposes, however, it is now much more satisfactory to study dried and stained preparations (*q. v.*), or to use the concentration method of Bass and Johns. A useful method, when hunting for malarial parasites in fresh blood, is to use at first an open diaphragm while quickly running over many fields with not too high a power, keeping a sharp lookout for minute *pigment-granules;* if pigment be found, an oil-immersion lens is turned in, and one determines whether the pigment is in a parasite, or in a leukocyte, or is merely an artefact.

In *tertian malaria,* the infected corpuscles show a marked pallor and an increased diameter; in *quartan,* and also in *estivo-autumnal,* infections, the red corpuscles containing the parasites look shrunken, and are of a deeper yellow color ("brassy corpuscles") than normal corpuscles. The character of the pigment differs in the different types of malaria also. (See Malaria).

The appearance in the blood of the other parasites above mentioned will be found described in connection with the several diseases (see Diagnosis of the Infectious Diseases). Most of these parasites can be far better studied in smear preparations stained by one of the methylene-azure-and-eosin stains (Wilson's or Giemsa's).

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6. The Microscopic Examination of Stained Blood

The introduction of *elective* or *differential staining* of the formed elements in the blood by Ehrlich revolutionized clinical hematology. Thin smears are made, dried in the air, fixed, stained, mounted, and studied under the oil-immersion lens.

(*a*) *The Preparation of Dry Films, or Smears, of Blood for Staining*

The blood is spread in thin layers, on absolutely clean slides, or on two cover-glasses, preferably the latter.

Cover-glass Method.—Both coverslips should be carefully dusted with a fine camel's-hair brush immediately before use. A *small drop* of blood, drawn from the fingertip, with observation of the details already described, is received on the middle of a thin, absolutely clean, fat-free, cover glass held in a pair of stiff straight forceps, and then immediately placed upon a second cover-glass held firmly fixed, beforehand, in a pair of strong, cross-billed forceps; in doing this, the upper cover-glass is placed so that its corners project over the edges of the under one (Fig. 302). No pressure should be applied. One waits a moment until the drop has nearly, but not quite, stopped spreading between the two cover glasses, and then, quickly seizing one corner of the upper cover with the straight forceps, pulls the two cover glasses quickly, but gently and smoothly, apart, in exactly parallel planes; sometimes both of the smears are good, sometimes only one; very often, for the beginner, neither.

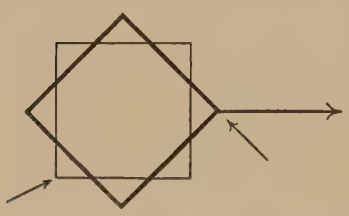

Fig. 302.—Preparing Cover Slip Smears of Blood. The Cover Slips Should Be Thin Enough for Oil-immersion Lenses.

In satisfactory smears, about 2/3 of the smear should be so that the individual red corpuscles show a uniform distribution, and do not overlie one another. Some workers prefer to hold the cover glasses in their fingers instead of using forceps; undoubtedly, with practice, good smears can so be made. Even when the cover slips are applied to one another with forceps, some prefer to pull them apart with their fingers.

Glass-slide Method.—Fairly good smears may also be made by receiving a larger drop of blood upon the end of a clean glass slide and pushing this—*not* pulling—obliquely along the surface of a perfectly clean and flat second slide, the blood droplet lying in the acute angle (45°) between the two slides. The blood spreads out in a thin film on the second slide. This is a much easier technic to acquire than the cover-glass method, but careful workers prefer the latter, as it ensures a more even distribution of the white cells in the smear. In studying a smear made

by the glass-slide method, it is to be remembered that the leukocytes tend to be more numerous in the periphery of the smear, and one must therefore study the edges as well as the central parts.

Preservation of Unstained Smears.—All the smears are allowed to dry thoroughly in the air, blood side up, protected from dust and flies (bell jar), after which they can, if desired, be kept for years. They are fixed before staining; if the smears are to be kept for some time before staining, it is better to postpone the fixation also, until just before they are stained. If the smears are to be stained by one of the Romanowsky methods, they must be fixed and stained within one week after the blood is drawn; if Ehrlich's triacid stain is to be used, the smears may be kept for several weeks or even months before fixing and staining. The dry smears should be placed in a small cardboard box, and labelled with (1) the name, (2) the date, and (3) the result of the count of the total number of white blood-cells made at the same time.

(*b*) *The Fixation of Blood Smears*

Some experience is necessary in judging of the size of the drop of blood to be used in making these smears. In normal blood, and in polycythemia, a small drop suffices; in the anemias, and in hydremia, a larger drop will be required.

i. Fixation by Heat

To fix the smears by heat, they should be kept at a constant temperature, of about 110° C. for 45 to 60 minutes, or longer; or at a temperature of 120°-125° C. for a few minutes.

One may use, for this purpose, a thermostat, set at 110° C. for the slower fixation, or at 125° C. for the more rapid fixation. A Victor-Meyer toluol-oven is very convenient.

A triangular copper plate (30 cm. long and 9 cm. broad), placed on a tripod and heated at its apex by a steady gas flame, may be employed for the fixation; after the temperature of the plate, in its different parts, has become fairly constant (about fifteen minutes), one places drops of water along its surface, beginning at the broad end and passing toward the apex, to determine the so-called "spheroidal-point line" for water on the copper bar, *i. e.*, the line farthest from the flame at which a drop of water rolls off immediately as a sphere (Leidenfrost's phenomenon); in the cooler parts of the bar, it sizzles and quickly evaporates. This "spheroidal-point line" corresponds to a temperature of 140°-150° C. The coverslips, with the smear side up, are placed just at the spheroidal-point line, and are generally well fixed in from 15 to 45 seconds.

The correct length of time for fixation has to be determined for each specimen of blood; for it varies with (1) the thickness of the smear, (2) the age of the smear, and (3) the type of blood to be examined.

In certain instances, a smear will be sufficiently fixed in 5 seconds; another may require 2 minutes.

This method of fixation is employed, especially, before using Ehrlich's triple stain or Pappenheim's carbol-pyronin methyl-green mixture. R. S. Morris makes the excellent suggestion that we place four smears on at once, and remove one at the end of 30 seconds, one after 35, a third after 40, and the fourth after 45 seconds, and then stain all four and see which one has the best fixation.

ii. Fixation in Absolute Ethyl Alcohol

After being air-dried, the smears are immersed in absolute alcohol for from 3 to 5 minutes, in an air-tight vessel, and are afterwards dried in the air. This method of fixation gives good results when followed by one of the methylene-azure-and-eosin stains (Romanowsky's, Giemsa's, Wilson's), though fixation with absolute methyl alcohol is more often used. even for these stains.

iii. Fixation in Absolute Methyl Alcohol

The coverslips lie 3 minutes in this fluid (2 minutes will suffice if the smears have been air-dried for 12 hours or longer) in a glass box with closely fitting cover (air-tight). The methyl alcohol should be really absolute.

This is the fixation method most often employed. It may precede the use of various stains (methylene blue, eosinate of methylene blue, hematoxylin and eosin, methylene azure). In Jenner's stain and in Wilson's stain, the dye-stuff is dissolved in absolute methyl alcohol; one does the fixation in the concentrated stain itself.

iv. Other Methods of Fixation

The three methods outlined above suffice for nearly all purposes. Acetone, alcohol and ether, acetone and methyl alcohol have all been used, but they are no better than those described. For the staining of mitochondria (Schridde, Freifeld) osmium-fixation is desirable. For fixing moist smears (not air-dried), Zenker, formol, or Schaudinn's sublimate-alcohol (2 parts conc. aq. solution $HgCl_2$+1 part absol. ethyl alcohol) may be used, the smears being left swimming on the fluid for from 12 to 24 hours.

Reference

Corper (H. J.). *A clinical electrical fixing and hot staining apparatus. J. Am. M. Ass., Chicago, 1915, lxv, 420.*

(c) *The Staining of Dried and Fixed Blood Smears*

Various parts of the white and red corpuscles show different chemical affinities for acid, basic or neutral dyes. The nuclei of the white cells, for example, show an avidity for basic dyes, probably because their contents are acid (nucleinic acid),

and they are therefore said to be "basophilic." In the protoplasm of many of the cells are granules, some of which stain intensely with basic dyes (*basophilic granules*), others intensely with acid dyes (*acidophilic* or *oxyphilic granules*, α-granules of Ehrlich), and still others with neutral dyes (*neutrophilic granules*, ε-granules of Ehrlich).

In addition to the chemical affinities of the constituents of the cells, the staining is influenced, also, by physical factors. Thus the method of fixation employed, and the particular staining procedure followed, may make a great difference in the result. The nuclei of lymphocytes, which, after fixation in absolute methyl alcohol, will stain with great intensity in methylene blue, lose the power to stain thus intensely in the same dye if the fixation has been done on the hot copper bar. It is no surprise, therefore, to find that the same variety of granulation in the white blood-cells may be stained different tints by one and the same dye-stuff, when different methods of fixation or of staining are employed.

In staining blood smears, one may use *simple stains*, containing only one dye-stuff, or *combined stains*, consisting of two or more dye-stuffs (acid, basic, neutral), and applied, either simultaneously, or successively. Thus, of the simple stains, we may mention (1) methylene blue, or (2) dahlia, used as single basic dyes, and (3) eosin, or (4) acid fuchsin, used as single acid dyes.

In the combined stains, the staining fluid contains basic, acid, and neutral dyes, mixed in certain proportions; from such mixtures of dye-stuffs, the several structures select the particular dyes for which they have an especial chemical affinity, or an especial physical relation. Thus, acid constituents will attract the basic dye-stuff (*basophilic staining*); alkaline constituents will select the acid dye-stuffs (*acidophilic* or *oxyphilic staining*); whereas constituents of the cell having both basophilic and acidophilic tendencies simultaneously, will attract both kinds of dyes, and stain in a mixed, or neutral, tone (*neutrophilic staining*).

Sometimes we use two different kinds of acid dye in the same combined stain, since it has been found that the different acidophilic substances in the formed elements of the blood may not behave alike to one and the same acid dye. To take a well known example: in Ehrlich's triple stain, there are two acid dyes (orange G, acid fuchsin) and one basic dye (methyl green) acting simultaneously; though the hemoglobin of the red corpuscles is acidophilic, and the eosinophilic granules in the white corpuscles are also acidophilic, in well-stained specimens the granules will be found stained a bright red color (in the acid fuchsin), and the Hb a dull buff color (in the orange G).

These combined, or "panoptic," stains are very delicate instruments, and require great care in their use, if satisfactory results are to be obtained. If the smear be badly made, the fixation imperfect, or the technic of staining faulty, disappointment will result; but, in successful preparations, there is a differentiation by the elective staining that brings joy to the heart of the hematologist!

For general clinical purposes, one of the Romanowsky stains (methylene azure and eosin), the Jenner stain (eosinate of methylene blue), and Ehrlich's triple stain, are especially recommended, the first giving the best pictures of the mononuclear elements, and of pathological cells, the second of the eosinophil granules, and the third of the neutrophilic granules. For nuclear pictures, and for blood parasites, the methylene azure and eosin stains are best; thus Wilson's stain is excellent (also Giemsa's and Leishman's).

Half a dozen stains will suffice for all clinical purposes, notwithstanding the fact that at least a hundred have been devised and lauded. It is far better for the clinician to become thoroughly familiar with the use of a few good stains than that he work indifferently well with a larger number. I advise strongly that physicians in general practice buy their stains *ready-made*. Reliable preparations are fortunately available in the market. In large clinical laboratories, however, many of the stains can be more economically home-made; for this reason, the formulae and methods of preparation of the more important solutions are here given. Only the purest dyes should be purchased; those supplied by Grübler (Leipzig) enjoy a good reputation. Many of the stains can be bought as dry powders or crystals, requiring only solution in methyl alcohol to be ready for use.

A synopsis of the best methods for staining individual histological elements in normal and pathological blood is given in the table on page 77.

i. General Remarks on the Staining of a Blood Smear

For some stains, notably the triple stain of Ehrlich, it will suffice to place a few drops of the staining fluid directly upon the surface of the heat-fixed smear as it lies on a piece of blotting-paper, or on the table. If the glass-slide method has been used, and one wishes to avoid using too much stain, the area to be covered with the stain may be circumscribed by first marking it out with heavy lines with a blue wax-pencil.

With the methylene-azure-eosin stains (Wilson, Giemsa), this method of applying the stain is unsatisfactory, on account of the troublesome precipitates that arise. When staining with these fluids, therefore, it is much better to let the cover slip swim on the surface of the dye in a small watch-glass.

Watch-glass Method (*Naegeli*).—In order not to use much of the dye, and to avoid the scum on its surface, one takes an empty watch-glass of suitable size, places the coverslip in it (smear-side down), and then allows the staining fluid to run in, through a pipet with a narrow opening, between the coverslip and the watch-glass (Fig. 303). Just enough staining fluid is used to float the cover-glass. By this method, the iridescent scum that forms on the surface of the dye does not come in contact with the smear, and specimens entirely free from precipitates and scum

SYNOPTICAL TABLE OF BEST STAINING METHODS FOR THE STRUCTURES IN THE BLOOD

	Fresh blood.	Methylene Blue.	Hematoxylin.	Dahlia.	Thionin.	Ehrlich's Triacid.	Eosinate of Methylene Blue (Jenner).	Methylene Azure-eosin (Leishman; Giemsa; Wilson).	Combined Jenner and Giemsa (or Wilson).	Carbol-Pyronin-Methyl-Green.
1. All details simultaneously.									++	
2. Mature neutrophil granules.						++	+	o		o
3. Young neutrophil granules.							+	+		
4. Eosinophil granules.....	+					++	++		+	o
5. Basophil granules (mast-cells).....		+		++	+	o (vacuoles)	+	+		
6. Myelocytes.....						++	+	+		
7. Myeloblasts.....								++	+	
8. Large mononuclears and transitionals; azure granules in lymphocytes								++		
9. Türk's irritation forms (pathological myeloblast of Naegeli).....								++		
10. Lymphocytes; plasma cells.		+	++					+		++
11. Polychromasia.....		++			+	o	+	+	+	
12. Basophilic granulation of erythrocytes.....		++			+	o	+	+	+	+
13. Cabot's rings; Howell's bodies.....	o					o		++		
14. Nuclear structure.....		++	++		++	o	+	+	++	
15. Nucleoli.....		+						++		++
16. Blood platelets.....	+					o	o	++	+	
17. Parasites.....	+				+	o		++	+	
18. Fibrin; hemoconia.....	+									

can be obtained. When the time of staining is up, the coverslip is quickly removed with forceps, and the staining-fluid washed off in distilled water. The smear is then dried, first between layers of smooth blotting-paper, and,

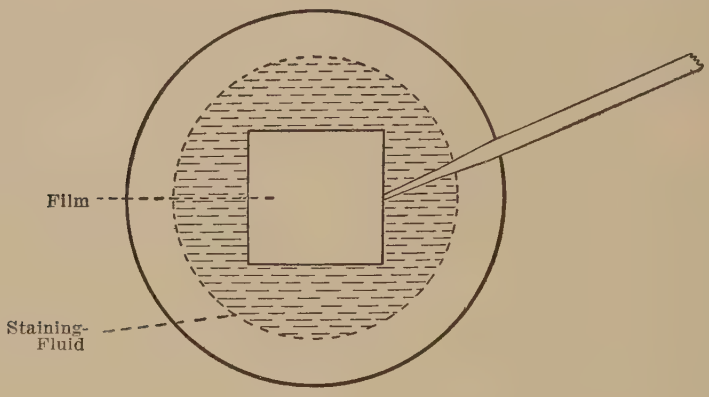

Fig. 303.—Watch Glass Staining of Blood Smears.

afterwards in the warm air, high above the flame. It is then imbedded in Canada balsam, which should be absolutely neutral, or the specimen will fade later; ordinary Canada balsam contains a trace of acid. Neutral Canada balsam can be purchased from Grübler.

ii. Simple Stains for Blood Smears

Occasionally a simple stain is required for some special purpose. Of these the more important are: (1) methylene blue; (2) eosin; (3) hematoxylin; (4) carbol-thionin; and (5) dahlia.

(1) Methylene Blue

The best stain to use is either the chemically pure medicinal methylene blue (¼-1 per cent aqueous solution), or the alkaline methylene blue of Löffler, used in all bacteriological laboratories.

(1) Fixation: Absolute methyl alcohol; absolute ethyl alcohol; or heat.
(2) Staining time: 5-20-120 seconds.
(3) Wash in running water, until the preparation assumes a light blue-gray tint to the naked eye.
(4) Press between folds of filter-paper to remove excess of water; then dry completely, by holding the smear, cautiously, high above the flame, between the thumb and forefinger.
(5) Mount in a drop of neutral Canada balsam.
(6) Examine under the microscope with oil-immersion lens (and Abbé-condenser).

The nuclei are stained deep blue, the red blood-cells greenish yellow, the basophil granules in the red corpuscles deep blue, and the polychromasic erythrocytes various shades of light and dark blue.

(2) Eosin

As a single acid dye, one uses eosin, in aqueous or alcoholic solution (0.5-1 per cent), or, if preferred, a weak aqueous solution of acid fuchsin.

(1) Fixation: Any method.
(2) Staining-time: 3-5 minutes.
(3) Wash in water, dry, and mount as above.

Red corpuscles, and acidophil (or eosinophil) granules, stain bright red.

(3) Hematoxylin

For hematoxylin stainings, there is nothing better than the ordinary Delafield hematoxylin of the pathological laboratories. The solution should be filtered before using. A hematoxylin stain alone shows the nuclei well, but it is so easy to counter-stain with eosin, that we nearly always use the double stain.

(1) Fixation: Absolute methyl alcohol, 3-5 minutes.
(2) Stain in half per cent alcoholic eosin solution by watch-glass method, 3-5 minutes.
(3) Wash with water; press between filter-paper; dry thoroughly in warm air high above the flame.
(4) Stain with Delafield's hematoxylin by watch-glass method, 3-5 minutes.
(5) Wash in water, dry, and imbed in neutral balsam.

All the nuclear structures are exquisitely stained. It is particularly useful in demonstrating the nuclei of the lymphocytes and of the lymphoblasts in the lymphatic leukemias. The nuclei of myeloblasts in acute myelogenous leukemia can also be well brought out.

The eosinophil granules are well stained, but the neutrophil granules are unstained. Nuclear particles stain intensely, a dark bluish purple.

(4) Carbol-thionin

This stain, introduced by Futcher and Lazear into hematological work, is a very useful one.

Sat. sol. thionin in alcohol (50 per cent)	10.0
Carbolic acid (1 per cent)	100.0

(1) Fixation: Alcohol-formalin.
(2) Staining-time: 15-120 seconds.

(3) Wash in running water; if over-stained, decolorize briefly in 50-per-cent alcohol.

(4) Dry thoroughly; mount in neutral balsam.

Nuclei dark blue; granules in polymorphonuclear basophils purple; R.B.C. greenish gray; basophil granules in R.B.C. dark blue; polychromasic R.B.C. in different shades of blue; protoplasm of malarial parasites, purple.

(5) Dahlia

It is best to buy the alcoholic solution of dahlia, ready made, of Grübler.

(1) Fixation: Heat; or absolute alcohol.

(2) Staining-time: 4 to 6 hours with watch-glass method.

(3) Wash quickly in water; too long washing may dissolve out the basophil granules.

(4) Decolorize in alcohol until dye ceases to be extracted.

This is the best method of staining the granules in polymorphonuclear basophils and in basophilic myelocytes. The granules are stained violet.

iii. Combined Stains for Blood Smears

We shall consider (1) Ehrlich's triple stain; (2) the eosinate-of-methylene-blue stains (Jenner, May-Grünwald); (3) the methylene-azure-and-eosin stains (Romanowsky, Leishman, Giemsa, Hastings, Wright, Wilson); (4) the combined Jenner and Giemsa stains (Pappenheim's "panoptic" stain); (5) carbol-pyronin methyl-green stain (Pappenheim-Unna); and (6) stains for the Altmann-Schridde granules.

(1) Ehrlich's Triple Stain

It was the introduction of this and similar stains, by Ehrlich, that led to the modern differential study of the formed elements of the blood. When the stain is properly prepared, and the fixation has been good, admirable results are obtainable, especially in the staining of the neutrophilic and eosinophilic granules. Many have found difficulty in securing a good staining fluid, and, for this reason, the tendency has been to abandon Ehrlich's stain for others that are less capricious. I believe that the method is now too little used. Every student of the blood should familiarize himself with this technic. Good stain can generally be secured, ready made, from Grübler, and for the practitioner, this is advisable. The stain may, however, thanks to the careful studies of Roger S. Morris, now be satisfactorily made in the laboratory. The modification introduced by Morris is the best one to follow, since it has been found to yield almost uniformly good staining mixtures.

The staining fluid contains three different dye-stuffs: methyl green, orange G, and acid fuchsin. Saturated solutions of each are made, and allowed to stand some time (at least a week), before use; it is best to use Grübler's dyes in making these solutions.

Morris's modified formula is as follows:

Saturated aqueous solution of orange G	13.0
Saturated aqueous solution of acid fuchsin	7.0
Distilled water	15.0
Absolute alcohol	15.0
Saturated aqueous solution of methyl green	17.5
Absolute alcohol	10.0
Glycerin	10.0

On mixing these fluids, the same graduated cylinder is used; it should not be rinsed between one fluid and the next. Each fluid is added in the order given above. It is essential that the methyl green, the second portion of the alcohol, and the glycerin be added slowly, and that the mixture be shaken well after each addition.

The staining fluid is ready for use immediately after preparation, and does not seem to deteriorate with age, though, after the mixture has stood for a time, a small amount of precipitate may form. In order that this precipitate may not be disturbed when using the stain, the bottle should never be shaken, and staining fluid should be taken from the center of the bottle with a pipet or with a glass rod.

Method of Staining

(1) Fixation: Heat is the only satisfactory method; a few preliminary trials may be required to determine the length of time the heat should continue for correct fixation. (The cover-glass should be air-dried for at least 24 hours before fixation.) Passable specimens can be secured after fixation for from 5 minutes to several hours in absolute methyl alcohol in an air-tight vessel, the fluid being changed several times (Sahli).

(2) Staining-time: 5 minutes; over-staining is impossible if the fixation has been correct.

(3) Wash under the tap until the washings are clear.

(4) Dry; mount in neutral balsam.

When the fixation has been correct, and the staining fluid is good, the cells are stained as follows: The *erythrocytes*, a buff, or yellowish orange, color; when over-fixed, these stain yellow; when under-fixed, they stain red. Polychromasic red corpuscles are not well shown; they may take a deep reddish-violet tint. The basophil granules of the R.B.C. and Cabot's rings are not stained. The *leukocytic granules are sharply differentiated;* the neutrophilic granules are lilac or reddish violet—by all odds, the most beautiful neutrophilic stain; the large eosinophil granules are brick-red, or copper-colored; basophilic granules dissolve out, and, at their former sites, one sees unstained "vacuoles." All the *nuclei* of the white corpuscles assume a feeble bluish-green shade. The nuclei of megaloblasts also stain feebly blue, but the nuclei of normoblasts are often more intensely stained. The *protoplasm* of the lymphocytes and of the large mononuclears stains faintly, the protoplasm being nearly colorless or assuming a shade of delicate rose pink, while the nuclei of these

cells generally take a pale greenish tint. The azure-granules of the lymphocytes are unstained. Malarial parasites are not stained.

A feature of the Ehrlich triacid preparations that deserves mention is the appearance of jet-black particles (Neusser granules) in many of the nuclei; they are artefacts.

Some workers subject the smears to a brief subsequent staining with methylene blue (¼ per cent aqueous solution) to increase the distinctness of the nuclear structures.

(2) The Eosinate-of-Methylene-Blue Stains (*Jenner; May-Grünwald*)

In 1899 Jenner published a method of staining, in which the chemical substance eosinate of methylene blue is used, asserting that it yields results very much better than those obtainable by successive staining with eosin and methylene blue. In 1902 a similar stain was introduced by May and Grünwald in Germany. In both cases, the fluid consists of the dye dissolved in methyl alcohol.

The chemical substance, eosinate of methylene blue, can now be bought in tablet (or tabloid) form from either Burroughs, Wellcome & Co., or from Grübler; all one has to do is to dissolve one tablet in 10 c.c. pure methyl alcohol (absolute, free from acetone), and the dye is ready for use.

The fluid stain can also be purchased if desired; it no longer pays to try to prepare the eosinate of methylene blue one's self.

If, however, one is out of the dye, and none is easily accessible, he can prepare it himself provided he has the ingredients, according to Jenner's second, simpler, method: 125 c.c. of a 0.5 per cent solution of Grübler's yellowish eosin in absolute methyl alcohol are mixed with 100 c.c. of 0.5 per cent solution of pure medicinal methylene blue (Grübler) in absolute methyl alcohol. The mixture is ready for use immediately, and the staining results are entirely satisfactory.

Since the dye is dissolved in absolute methyl alcohol, the fixation and the differential staining are both done with the staining fluid. It is desirable (1) that the smears should be thin, and (2) that they should be fixed and stained at once, that is, as soon as they have been made and dried in the air.

Technic.—The actual technic for using Jenner's stain will vary with individual specimens of the dye, but the general method is as follows:

(1) Fixation: Cover the air-dried, but unfixed, blood smear for 2-3 minutes (not longer) with 8-10 drops of *undiluted* staining-fluid, or, better, float it upon the fluid by the watch-glass method, measuring exactly the quantity used.

(2) Staining: Add distilled water, equal in volume (drops) to that of the pure staining-fluid used for fixation; mix the fluids in the watch-glass, thoroughly, by sucking them into a pipet and blowing them out under the coverslip several times; stain for from 2-5-10-15 minutes.

(3) Wash quickly in a glass of ordinary water, or longer in distilled water, until the smear is of a rose color.

(4) Dry; mount in neutral balsam.

Old smears are difficult to stain. Naegeli advises then the following method:

(1) Fixation: Absolute ethyl alcohol, or absolute methyl alcohol, 10-20 minutes.

(2) Staining: Float smear, by watch-glass method, on a mixture of the Jenner staining-fluid (1 part) and distilled water (2 parts) for from 5-15 minutes. Then wash, dry, and mount as above.

All nuclei stain blue. The granules of the polymorphonuclear basophils (mast-cells) are well shown, as they stain violet (metachromatically). The eosinophil granules are beautifully stained scarlet; it is one of the finest ways of staining them. Mature neutrophil granules stain fairly well; immature neutrophil granules are imperfectly stained, sometimes not at all.

As a rule the azure granules of the lymphocytes are not stained, but occasionally, probably owing to a little methylene azure in the dye, they may be stained.

The protoplasm of the large mononuclears and transitionals stains strongly blue; it is often difficult to distinguish a large mononuclear from a lymphocyte of the same size, in smears stained by Jenner's method.

The polychromasic R.B.C., and basophilic granules in abnormal R.B.C. show up well; Cabot's rings are not stained.

Jenner's stain is better than the Romanowsky stains for demonstrating the leukocytic granules, but it is surpassed for this purpose by Ehrlich's stain. On the other hand, it is superior to the latter for revealing the nuclei and the abnormalities of the red cells, but inferior to the Romanowsky stains for these purposes. It is a very popular stain, however, and on account of ease of preparation, and the admirable pictures it yields, it has large vogue among general practitioners.

(3) The Methylene-Azure-and-Eosin Stains (*Romanowsky, Nocht, Leishman, Giemsa, Hastings, Wright, Wilson*)

These are admirably adapted for the routine examination of the blood, and are especially valuable for the demonstration of nuclei, azure granules, malarial parasites, other blood parasites, and abnormal changes in the red cells. These stains are all outgrowths of a stain introduced by Romanowsky in 1891, and they are, as a group, accordingly, often referred to as "the Romanowsky stains." They include the Romanowsky, Ziemann, Nocht, Leishman, Reuter, Michaelis, Hastings, Wilson and Wright stains. It has turned out that the specific qualities of these stains depend chiefly upon the presence of methylene azure and eosin in the several staining fluids.

The original Romanowsky stain is no longer in use. In the clinic in which I work, Giemsa's stain and Wilson's stain are the two forms chiefly used, and I shall describe them fully. In other clinics, Leishman's, Hasting's, and Wright's stains enjoy a good reputation, so that they also will be taken up briefly.

(a) **Giemsa's Stain.**—In 1902, Giemsa taught us how to make a

methylene-azure-eosin stain that is far superior to any of the Romanowsky stains that preceded it. The formula is as follows:

Azure II eosin (Grübler)	3.0
Azure II	0.8
Glycerin	250.0
Methyl alcohol (absolute)	250.0

The dyes are ground up in fine powder and mixed with the methyl alcohol, the glycerin being added afterward. This stain is a very difficult one to prepare, and certainly the beginner should not attempt it, but should buy it ready-made.

(1) Fixation: In absolute methyl alcohol, immediately after air-drying, 3 minutes. If air-dried for 24 hours, fix for 2 minutes. Absolute ethyl alcohol, 20 minutes, also gives a good fixation.

(2) Staining: Smear to be thoroughly dried after fixation. Float on a dilution of the Giemsa stain (10-15 drops to 10 c.c. distilled water), by the watch-glass method, for 10-30-60 minutes. The staining-time affects the result; brief staining (5-10 minutes) yields good nuclear pictures but poor granule-staining; longer staining (30-60 minutes) yields good azure-granule staining but poor nuclear staining, especially of the lymphocytes.

When staining especially for parasites, 1 or 2 drops of a 1-per-cent solution of potassium carbonate may be added to the 10 c.c. of diluted stain.

(3) Wash under the tap; dry thoroughly; mount in neutral balsam.

The smears should be thin; the watch-glass method of staining is especially important here in order to avoid the iridescent scum.

The Giemsa stain is certainly one of the best in use for blood smears, since it gives beautiful nuclear pictures and stains the azure granules well, though it is disappointing for the neutrophilic granules.

Nuclei, red or bluish; pycnotic nuclei, blue; nucleoli, a beautiful deep blue.

Neutrophilic granules, violet red in the older cells, dark purple-violet, sometimes reddish brown, in the younger cells, usually poorly differentiated; eosinophil granules, dull reddish brown (sometimes unsatisfactory); granules of polymorphonuclear basophils (mast-cells) are usually dissolved out, though if any remain they stain violet.

The protoplasm of the lymphocytes stains pale blue, and (in $\frac{1}{3}$ of the cells) contains a few coarse red azure granules. The protoplasm of the large mononuclears and transitional forms takes a pale bluish stain, and contains in the best-stained specimens, a great number of exceedingly minute red granules. These granules may be so numerous as to obscure the pale blue protoplasm, in which they are imbedded. There is no more beautiful way of staining these large mononuclear and transitional forms.

The polychromasic red corpuscles stain blue; basophil granules in the red corpuscles stain deep blue, though in the severe forms of anaemia they may stain red; sometimes red and blue granules are seen in the

same erythrocyte. Nuclear particles in the erythrocytes (including Howell's bodies), stain intensely red and stand out sharply on the bluish background of the polychromasic red corpuscle. Cabot's rings also stain intensely red; though the smears should remain in the stain for from 30-60 minutes to get the best results with these.

(b) **Wilson's Stain.**—Wilson's method is uniformly satisfactory for the particular purposes for which it is adapted. It is relatively easy to carry out, and is somewhat more economical than others. The essential components of the stain are eosin and methylene azure, the latter being made by oxidizing an alkaline solution of methylene blue.

I am indebted to Dr. Sydney R. Miller for the following account of the method for preparing Wilson's Stain as used by him:

Two solutions are required:

Solution A:

Methylene blue	2.0
Silver oxid	2.0
Sodium bicarbonate	1.0
Distilled water	200.0

Solution B:

Eosin (yellow-soluble in water)	1.0
Distilled water	200.0

To prepare the silver oxid, 2.0 gms. of silver nitrate are dissolved in 15 c.c of distilled water, after which 260 c.c. of a freshly prepared solution of calcium hydrate are added. The mixture is well shaken and set aside until the precipitate falls. Silver oxid is precipitated according to the equation: $2AgNO_3+Ca(OH_2=Ag_2O+H_2O+Ca)_2(NO_3)$. The brown precipitate is collected on a coarse paper-filter, washed in a little distilled water, and dried in a hot-air oven at a temperature not exceeding 80° C. On theoretical grounds, the amount of silver oxid that should be recovered by using the amounts above given is 1.365 gms. This should be kept in a well-stoppered brown bottle; so kept, it works perfectly well for a long period of time. To prepare the solution of $Ca(OH)_2$, it is necessary only to purchase a small amount of ordinary unslaked lime, to slake it with two or three liters of distilled water, stirring well and allowing it to settle; the upper layer, which contains various impurities, notably carbonates, is siphoned off; then add two or three liters of fresh water, mix again and repeat as above; the fluid from the third washing is used in preparing the silver oxid.

Having prepared Solution A in the manner just described, it is boiled in a relatively deep porcelain dish. The boiling should be continuous and slow, the solution meanwhile being stirred occasionally. At the end of 20 minutes an amount corresponding to about 1/3 of the original volume is decanted into a graduated cylinder, and an equal amount of distilled water is then added to the original solution, which is kept boiling for another 20 minutes; the water should be hot when added. At the end of this second period of time, one half of the contents of the porcelain dish is poured into the same graduated vessel, after which the boiling is continued for another 20 minutes, without any further addition of water. The solution remaining in the porcelain dish is now added to the other two fractions and enough distilled water added to bring the total volume

up to its original amount. This solution is filtered at once through a coarse filter into a suitable beaker and Solution B is immediately added. The two fluids are mixed well, and at the end of from 15 to 30 minutes, the resultant deep, rich, burnt-reddish-brown precipitate is filtered off on a *hard* filter-paper. The filtrate should be transparent when it comes through and of a watery blue color, showing definite fluorescence. From time to time during the filtration the sides of the filter should be washed down with small amounts of normal sodium-chlorid solution.

The precipitate may be dried in one of three ways:

(a) In the air. This takes a long time.

(b) By suction.

(c) Preferably, in a hot-air oven at a temperature of 60° to 80° C.

The dark, bluish-black powder thus obtained has a bright greenish luster; it should be kept in a dark bottle, carefully sealed, and away from light. The average yield of dry precipitate from the quantities of ingredients mentioned is 1.5 to 1.9 gms. This yield could probably be increased somewhat by using a little more eosin in Solution B and with an increasing brilliancy in the resultant stain.

To make the staining fluid, 0.4 g. of the stain are dissolved in 100 c.c. of pure (absolute) methyl alcohol. It is best to make up only a little at a time, as the stain does not act well if it be over three months old.

Technic of Wilson's Stain.

(1) Fixation: The air-dried, unfixed, smear is floated (by the watch-glass method) on 6-8 drops of the stain for exactly one minute. It is not necessary to use the watch-glass method and many workers do not resort to it but simply place a few drops of the staining fluid upon the smear.

(2) Staining: Add an equal quantity of distilled water to dilute the stain; staining-time, 4 minutes. (A superficial iridescent scum forms on the surface after the addition of the water; the watch-glass method prevents this from contaminating the smear.)

(3) Seize the cover-glass with forceps, remove quickly from the stain, wash in water, dry thoroughly, and mount in neutral Canada balsam. Even if one stain the smear without the watch-glass method, the unsightly precipitates may largely be avoided, on washing off the stain, by allowing water to flow on, and to float off from the smear all of the stain, the film being held all the time in a horizontal position. The smear should be washed in distilled water until, when held against a white background, it shows a faint, pinkish-brown or tan shade.

The results obtained by Wilson's stain are practically the same as those described above for Giemsa's stain. The main differences are mentioned in the footnote on page 114.

The sources of error on using Wilson's stain have been well summarized by R. S. Morris: (1) Too great dilution gives rise to poor nuclear staining; (2) a trace of acid in the dilution-water, in the wash-water, or even acid fumes in the room, may ruin the specimen; (3) a trace of acid in the staining-fluid is fatal to the stain; this fault may be remedied by adding a few drops of absolute methyl alcohol containing a little dissolved KOH (by alcohol); too much should not be added, or it will be necessary to titrate back with absolute methyl alcohol con-

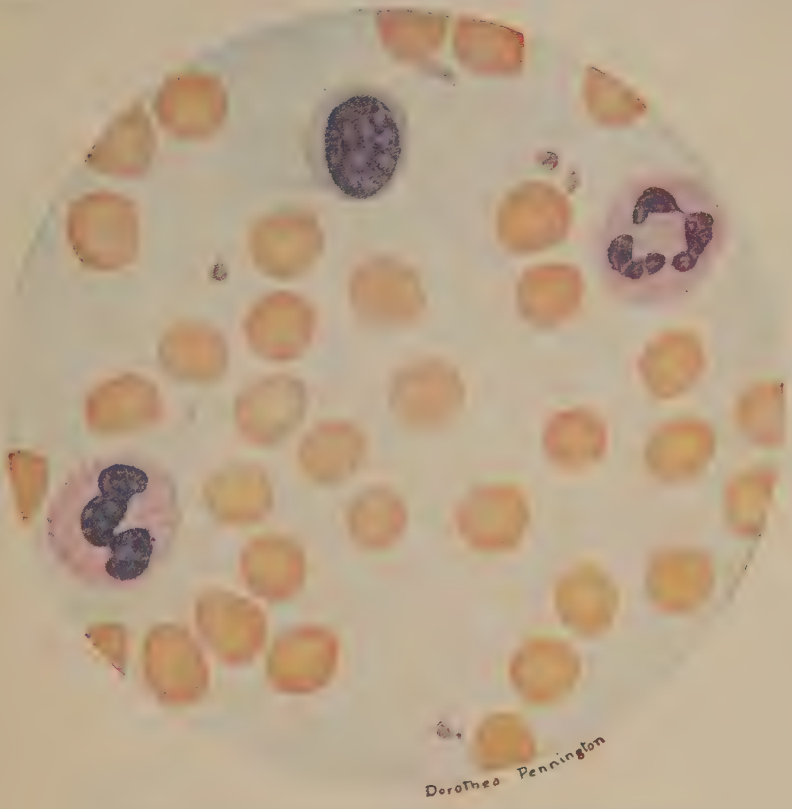

Fig. 1.—Normal Blood. Wilson Stain. (Original Drawing.)

Fig. 2.—Trichinella spiralis Embryos in the Blood. Acid eosin-methylene-blue Stain. (After Stäubli, in Mohr u. Staehelin's "Handb. d. inner. Med.," published by J. Springer, Berlin.)

taining a trace of glacial acetic acid (Peebles and Harlow); and (4) the stain may be extracted from the basophil elements by washing too long after staining.

(c) **Leishman's Stain.**—The stain should be bought, ready-made, from Burroughs, Wellcome & Co., or from Grübler. It can be obtained in liquid form, or in tablets (0.2 gram), to be dissolved in 10 c.c. absolute methyl alcohol.

(1) Fixation: By floating on 10 drops of the strong solution (watch-glass method) for one minute.
(2) Staining: Add an equal volume of distilled water; mix thoroughly by drawing the fluid into a pipet and blowing it out again, repeating several times; staining-time, 4 minutes.
(3) Wash under the tap; dry thoroughly; mount in neutral balsam.

The results obtained are practically identical with those yielded by Giemsa's stain, but the mast-cells are sometimes better preserved.

(d) **Hasting's Stain.**—This also is a good Romanowsky stain. It should be bought, ready-made, from E. Leitz, New York City.

(1) Fixation: By floating on 8-10 drops of the strong concentrated staining-fluid for one minute.
(2) Staining: Add an equal volume of distilled water to dilute the stain; staining-time, 2 minutes.
(3) Wash in distilled water; dry; mount in neutral balsam.

(e) **Wright's Stain.**—The method of preparing this stain will be found in an article in the J. Am. Med. Ass., Chicago, 1910, lv, 1979. It is another of the methylene-azure stains.

(1) Fixation: In the concentrated staining-fluid (watch-glass method) one minute.
(2) Staining: Add an equal volume of distilled water with a pipet, mixing thoroughly; staining-time, 2-3 minutes.
(3) Wash in water for 30 seconds or longer, until the thinner part of the film is yellow or pink; dry thoroughly; mount in neutral balsam.

The erythrocytes are orange or pink; the nuclei of the leukocytes are stained blue or violet-blue; the neutrophil granules are lilac; the eosinophil granules red or pink; the granules of the polymorphonuclear basophils deep blue or purple. The protoplasm of the lymphocytes is light blue; the blood platelets, deep blue or purple. Protoplasm of the malarial parasites blue; the chromatin masses lilac, ruby red, or blue; bacteria blue. Polychromasic red cells stain blue; the basophil granules in the red corpuscles stain blue.

This is a good general stain, but, like the other stains of the group, may be unsatisfactory for the neutrophil granules.

(4) Combined Jenner and Giemsa Stain (*Pappenheim's Panoptic Stain*)

(1) Fixation: Air-dried, unfixed smears floated on concentrated Jenner staining-fluid (by watch-glass method), 3 minutes.

(2) Staining: (a) Add an equal volume of distilled water to dilute; staining-time, 1 minute.

(b) Pour off the diluted Jenner stain; do not wash the smear, but float it on dilute Giemsa solution (15 drops of Giemsa stain to 10 c.c. distilled water); leave for 15 minutes.

(3) Wash thoroughly in tap-water; dry between filter-paper, and then in the air, but not over the flame; mount in neutral Canada balsam.

(5) Carbol-Pyronin Methyl-Green Staining (*Pappenheim-Unna*)

This fluid contains two basic dyes:—pyronin, which stains basophil substances intensely red; and methyl green, which is a specific basic stain for nuclear chromatin.

The dye should be bought ready-made.

(1) Fixation: Heat, or absolute methyl alcohol.
(2) Staining: In the concentrated solution, 5-10 minutes.
(3) Wash thoroughly under the tap; dry; mount in neutral balsam.

The protoplasm of the lymphocytes is stained intensely red, as is also the protoplasm of the plasma cells, and of Türk's irritation forms (pathological myeloblasts); markedly polychromasic R. B. C. stain red.

Nuclei of lymphocytes stain bluish-green, those of polymorphonuclear leukocytes more violet. It is asserted that a cell whose protoplasm does not stain bright red cannot be a lymphocyte.

Nucleoli are stained red, though the rest of the nucleus is blue. The nucleoli stain best after fixation for one minute on the copper bar and prolonged staining for several hours (Butterfield).

(6) Stains to Demonstrate the Altmann-Schridde Granules (*Mitochondria*)

Two methods are employed for this (1) Schridde's method, and (2) Freifeld's method. The details of these two methods are to be found in O. Naegeli's *Blutkrankheiten und Blutdiagnostik,* 2nd edition, 1912, pp. 30-32.

In smears stained by Schridde's method, the eosinophilic granules are reddish-black, the neutrophils pale brownish-red, the basophils colorless like vacuoles; the lymphocytes contain perinuclear yellowish or carmine-red granules or rods.

By Freifeld's method, the lymphocytes show an unstained protoplasm,

except that it contains intensely red points and rods—the so-called acidophil Schridde-Altmann granules.

The myeloblasts, stained by either method, contain peculiar red streaks and loops that are often very similar to the fuchsinophil granules of the lymphocytes, but the myeloblasts, it is asserted, are distinguishable from the lymphocytes in that the streaks and loops are present in large numbers, and diffusely throughout the protoplasm, not limited to the perinuclear region.

A whole series of methods has been worked out for staining the blood cells in *sections* of the hemopoietic organs. For these the reader is referred to Naegeli's treatise.

(*d*) *Staining of Unmixed Blood* (*So-called "Vital" Staining*)

There is some discussion as to whether we have to deal here with a true "vital" staining, or with the staining of dying cells.

Method of Pappenheim.—1. With a glass rod, spread a thin layer of a solution of the dye (cresyl blue in absolute alcohol; neutral red; carbol-pyronin-methyl-green), and let it dry. Hence the name, "dry method."

2. Make a fresh blood preparation in the ordinary way, but place the cover glass, blood-droplet down, on the thin layer of dry stain, instead of upon a clean slide. Seal with vasclin.

Method of Widal, Abrami and Brulé.

(1) Collect a little blood in a pipet and quickly dilute it with 10 times its volume of the following isotonic solution:

Unna's polychrome methylene blue....10.0
Solution of sodium chlorid (8 per cent).10.0
Solution of sodium oxalate (2 per cent). 1.0

Mix thoroughly and allow to stand for 10-15 minutes.

(2) Centrifugalize; spread a little of the centrifugate on a glass slide. Dry in the air. Fix now with heat; mount.

Method of Vaughan.

(1) Puncture the ear; wipe away the first drop of blood; then quickly with a glass rod, apply over the puncture wound a minute drop of Unna's polychrome methylene blue and allow a small drop of blood to mix with the stain.

(2) Make from this mixture of blood and stain, a fresh preparation with cover glass and slide, in the ordinary way. Seal with vaselin. Examine with oil-immersion lens.

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7. The Red Blood-Corpuscles in Dried and Stained Smears

We shall consider: (1) the morphology of the ordinary, non-nucleated corpuscles (erythrocytes), (2) that of the nucleated red corpuscles (erythroblasts), and (3) certain deviations from the normal appearance of stained red corpuscles.

(*a*) *Non-nucleated Red Blood-Corpuscles* (*Erythrocytes*)

Size.—These average 7.5 μ in diameter, in the normal adult, but may vary in size between 6 and 9 μ under normal conditions. Normal cells stain with acid dyes (eosin, orange G., acid fuchsin). In mixtures of acid fuchsin and orange G (as in Ehrlich's triple stain) the corpuscles "prefer" the orange G. This normal acidophil tendency is known as orthochromatic

staining; under pathological conditions, some of the R. B. C. become polychromatophilic (see below).

Anisocytosis.—The normal erythrocytes show scarcely any variations in their size and shape. When marked differences in size occur, the condition is spoken of as *anisocytosis*: there one may find all sizes of cells, from the small *microcytes* (1-6 μ), to the large *macrocytes* (9-16 μ), or even larger cells, measuring even up to 25 μ in diameter (*gigantocytes*).

Measurements of the Corpuscles.—In making *measurements of the diameter of red corpuscles* in stained films, we use an ocular micrometer, draw out the tube of the microscope to 160 mm., and control the values of the divisions of the micrometer scale in the ocular with the rulings in the Bürker counting-chamber, where the side of each of the smallest squares is 1/20 mm. (= 50 μ) long. If anisocytosis exist, we measure the diameter of 200 cells, and count the percentage of normocytes (6-9 μ), microcytes (1-6 μ) and macrocytes (over 9 μ).

Poikilocytosis.—When the red cells of either small or large size show irregularities in their outline, they are designated as *poikilocytes*. These may have arisen, either as the results of pressure exerted at the time the smear was made (artefacts), or from true pathological conditions (severe anemias), the poikilocytes then circulating in the blood as such. In chlorosis, when the Hb is below 40 per cent, mild poikilocytosis is common; also in the severer "secondary" anemias (carcinoma, ulcers, hemorrhoids, nephropathies) it is often seen. But it is most outspoken in the severe hemolytic anemias. Poikilocytosis associated with many macrocytes and the occurrence of many megaloblasts is one of the striking features of the blood in so-called pernicious anemia (Addison-Biermer type of hemolytic anemia), and may exist when the Hb-content is as high as 60-70 per cent; now and then, poikilocytosis may be slight, even in an extreme case of "pernicious" anemia (Naegeli). On the whole, the diagnostic significance of poikilocytosis is slight; it indicates anemia, but tells us by itself, nothing of the type.

(*b*) *Nucleated Red Blood-Corpuscles* (*Erythroblasts*)

These nucleated red corpuscles, always present in the normal red marrow of the bones, never occur under normal conditions in the circulating blood. They are often to be found in the circulating blood, however, in pathological states (anemias), and are the best evidence we have of a heightened regenerative activity on the part of the bone-marrow, of an "accelerated erythropoiesis." In certain severe anemias, the marrow loses its regenerative power; such anemias are known as aplastic, or aregeneratory anemias (*q. v.*). The erythroblasts, for convenience of description and on account of their origin and significance, are subdivided into three groups: (1) normoblasts; (2) megaloblasts; and (3) intermediate forms.

i. Normoblasts

The normoblasts (Pl. XIV) are of the same size as an ordinary R. B. C., or a little larger, and may show either orthochromatic, or polychromatic, protoplasm, according to their age; occasionally, they contain sharply-circumscribed basophil granules.

The nucleus, usually round, varies a good deal in size and shape; sometimes it is eccentrically placed. It has a strong affinity for basic dyes, staining often very intensely, by reason of its pyknotic structure. The nucleus may occasionally show a true chromatin net-work, often of the wheel-spoke type (younger forms). The older pyknotic forms often show evidences of nuclear fragmentation (karyorrhexis). Two or more nuclei may be present; occasionally, karyokinetic figures are seen.

Unusually small normoblasts are known as microblasts. In severe anemias, the protoplasm of the erythroblasts is rarely orthochromatic, but instead is to a variable degree polychromatic; the younger forms, with nuclei showing chromatin network, are mostly polychromatic, while the older forms, with pyknotic nuclei, approach to orthochromasia.

ii. Megaloblasts

These are large, nucleated, red cells with abundant, markedly polychromatophil protoplasm, and large, round or oval, rather feebly-staining, nuclei, the nucleus alone being as large as, or larger than, an ordinary erythrocyte. The nucleus generally exhibits an exquisite chromatin network, and a nuclear membrane. In fresh preparations, these megaloblasts may show ameboid movements (Thayer).

Along with a large number of macrocytes in the blood, the appearance of megaloblasts is characteristic of the blood of the Addison-Biermer type of hemolytic anemia. But megaloblasts and macrocytes may occur (in small numbers) in the blood in other hemolytic anemias, and, occasionally, even in posthemorrhagic and in myelopathic anemias; they are not uncommon in the anemias of children, though, more often, large young normoblasts are here mistaken for megaloblasts (see below).

The megaloblasts correspond to the nucleated red corpuscles of early embryonic life (*q. v.*); a few megaloblasts do occur in the normal marrow of adults (Grawitz, Bunting), but, as we have seen, erythropoiesis in normal adults is carried on, almost wholly, by normoblasts.

iii. Intermediate Forms of Erythroblasts

These forms cannot easily be classified in either of the other two groups. Some think that all the erythroblasts have a common origin, that some of the descendants of the primitive cell become normoblasts, some of

Normoblasts, Intermediates, and Megaloblasts with Wilson and Ehrlich Stains. × 800.
(Original Drawing.)

them megaloblasts, and that intermediate forms are an indication of imperfect differentiation, or development, in one or the other direction. Others believe that the normoblasts are derived from cells of the megaloblast-type, and that, in this derivation, they pass through stages corresponding to the "intermediate" forms. Usually the character of the nucleus (size, network, intensity of staining) will permit one to place an unusual type of erythroblast in either the normoblastic or the megaloblastic group, or the size and staining of the protoplasm may suffice for this; thus, an older megaloblast, whose nucleus is becoming pyknotic, may present a nucleus resembling much that of a normoblast, but it lies in a large, broad orthochromatic protoplasm; or, again, a large young normoblast may betray its nature by its small amount of protoplasm (markedly polychromatic) and its typical normoblastic type of nucleus, filling up most of the cell. The tyro should be cautioned against designating these large normoblasts as megaloblasts, simply on account of their size. It is quite likely, as Naegeli suggests, that many of the "megaloblasts" described as occurring in forms of anemia other than the Addison-Biermer type, and, especially, in anemia pseudoleukemica infantum, and in the myelopathic anemias (*e. g.*, carcinosis of the bone-marrow) have been, in reality, the large young normoblasts ("macroblasts") so commonly found in such conditions.

Both megaloblasts and normoblasts get rid of their nuclei in the same way (intracorpuscular karyolysis or karyorrhexis).

Some authors have suggested that both of the main forms of erythroblasts are derived from lymphocytes, the smaller lymphocytes giving rise to normoblasts, the larger lymphocytes to megaloblasts; but the evidence for this view is insufficient. The view advanced by Schridde, that the megaloblasts are the direct descendants (first generation) of the cells of the walls of the blood vessels, and that the normoblasts represent a second generation, would seem more probable.

iv. Blood Crises

Sudden, transitory "flooding" of the blood with erythroblasts is occasionally met with when the bone-marrow is stimulated to great regenerative activity. I have known periods when several hundred thousand normoblasts temporarily were present in a cubic millimeter of blood. Such "spurts" of regenerative activity are known as "blood crises."

The opposite phenomenon is seen when, in a severe anemia with fair regenerative activity, there is a sudden suppression of erythropoiesis, with rapid disappearance of all erythroblasts from the circulating blood. I am accustomed to speak of this phenomenon as a "negative blood crisis."

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(c) *Deviations from the Normal Appearance of Stained Red Blood-Corpuscles*

We have now to consider: (1) diffuse basophilic staining of the protoplasm of the red corpuscles (polychromasia), and (2) local basophilic stainings in the red corpuscles (basophilic granulation, larger nuclear fragments, Howell's bodies, chromatin dust, Cabot's rings, red granules, red filaments, etc.). These abnormalities are best seen, when present, in smears stained with Wilson's or with Giemsa's stain.

i. Diffuse Basophilic Staining of the Erythrocytes and Erythoblasts (Polychromatophilia; Polychromasia)

Some of the erythrocytes, under abnormal conditions, instead of staining orthochromatically, show a tendency to take up basic dyes, and for this reason are called polychromatophilic cells. The degree of polychromasia varies, from slight grades in which the basic stain is just visible, to those in which there is an intense staining with the basic dye alone. This polychromasia, seen best in simple methylene-blue stainings, though well shown also in smears stained with Wilson's, Giemsa's or Jenner's stains, occurs in two distinct types (a) the diffuse type to which the term polychromasia is usually restricted, and (b) the punctate type. This latter type is commonly referred to as *basophilia,* or as *basophilic granulation* of the red corpuscles, and is characterized by the presence, in the body of the red cells, of granules, varying in size and shape, which stain with the basic dyes. It will be described separately a little further on.

One of the best ways to become familiar with the appearance of polychromasic cells is to make a smear of red marrow, where large numbers of non-nucleated erythrocytes, and also numbers of erythroblasts, show a greater or less degree of polychromasia. In clinical work, we have frequent opportunity, in the various anemias, to study these polychromasic cells, both nucleated and non-nucleated, in the circulating blood. When they were first observed by Ehrlich, they were believed to be signs of degeneration, or of coagulation necrosis, of the red corpuscles, but we now know them to be, at least in the majority of cases, simply evidences of the youth of the cells, though of course it is possible that these young cells may be less resistant than normal cells to various noxae.

It is also true that polychromasia may sometimes be a sign of senility, or of actual degeneration, of red corpuscles.

Marked polychromasia does not mean, necessarily, a lack of hemoglobin in the red blood-corpuscles (Naegeli), for in marked polychromatic blood, such as that seen in the hemolytic anemias, the color-index may be high; and this is said to be true, even when macrocytes are not present in the blood.

In some cases of severe anemia, besides the common form of deep blue polychromasia, one sees, with Wilson's stain or with Giemsa's stain, certain red corpuscles colored entirely red (Naegeli, Ferrata and Viglioli). This so-called "azurophil polychromasia" has been thought to be due to a diffusion of nuclear chromatin throughout the protoplasm, but Naegeli leans to the view that it is merely a peculiar staining of certain grades of polychromasia, depending upon special physical-chemical influences.

ii. Local Basophilic Staining in the Erythrocytes

In the protoplasm of red blood-corpuscles either orthochromatic, or polychromatic, local areas, stained in basic dyes (basophil substances), may often be met with in pathological states, and a knowledge of them and of their significance, is important in clinical hematology. For the most part, they represent appearances due to the process of development of erythroblasts into erythrocytes, but the exact significance of many of these phenomena is as yet not fully understood.

(1) *Nuclear Fragments*

Fragmenting nuclei of erythroblasts are frequently seen, when either normoblasts or megaloblasts are present in the blood. This fragmentation of nuclei is technically known as *karyorrhexis.* Sometimes one sees a number of separate fragments; sometimes, the fragments are arranged in rosette-like nuclear figures; sometimes minute pieces seem to have been pinched off from the main mass of the nucleus. They stain as nuclei do (red, or blue, in Wilson's, or in Giemsa's, stain; blue in carbol-pyronin methyl green; purple in hematoxylin).

Such nuclear particles are present in the forms of anemia in which normoblasts and megaloblasts are most abundant (toxic anemias, Addison-Biermer anemia, anemias of childhood, etc.). They are, as might be expected, most abundant at the time of a blood crisis.

(2) *Howell's Bodies*

These are small particles, larger than ordinary granules, and smaller than ordinary nuclear fragments, but they undoubtedly represent nuclear remains, since they stain like the chromatin of nuclei (bright red or blue in Giemsa's, or in Wilson's stain; purple in hematoxylin). They are always perfectly round, and are sharply circumscribed from the rest of the corpuscle. Usually, only one body is present, though sometimes two may be seen. In rare instances, multiple Howell's bodies are met with in a single cell. They are more often seen in orthochromatic corpuscles than in the polychromatic forms. Occasionally they are accompanied by typical basophilic granulation.

The physiologist, W. H. Howell, observed them first in the posthemorrhagic anemia of cats; in Germany, they are described as the "Howell-Jolly bodies." They have been especially carefully studied by R. S. Morris in experimental anemias, who saw them, sometimes, when the nucleus of the erythroblast seemed to be quite intact. They have been noticed, by Naegeli, in lead poisoning, even when no anemia accompanied it.

(3) *Chromatin Dust*

Sometimes one sees at or near the extreme periphery of red corpuscles, single, minute, bright red granules in specimens stained by Giemsa's or by Wilson's stain. These are very much smaller particles than Howell's bodies, but probably represent a still later stage of the reduction of nuclear chromatin (Weidenreich). Occasionally, such particles are double, or multiple. They have been thought by some observers to be centrosomes, but there is no support for this opinion, nor is it probable that, as has been suggested, they are extruded from the corpuscles to form hemoconia. Most probably, they ultimately dissolve up in the cells.

(4) *Cabot's Rings*

The internist, Richard Cabot, of Boston, described, in 1903, remarkable bodies in the red corpuscles in certain cases of anemia. They assume the form of round rings, loops, figures of eight, etc. Sometimes several rings are visible in a single corpuscle, or one ring may be seen broken up into parts. These figures are now generally described in the literature as "Cabot's ring-bodies," or, simply, as "Cabot's rings."

They have been observed in the blood of the severer anemias (Addison-Biermer type, anemia pseudoleukemica, lead poisoning, acute leukemia). They are almost never seen in orthochromatic corpuscles, but always in markedly polychromasic cells. It is very common to see basophilic granules, or one or more of Howell's bodies, in the same cell. These rings are best demonstrated with Giemsa's stain or with Wilson's stain. The smears should be very thin, and the staining prolonged. Sometimes, they can be seen, in Wilson specimens, unstained within the polychromasic cells. It is asserted that they are fairly well-stained, also, with carbol-pyronin methyl green; both red and green rings appear (Ferrata). They can also be stained in Heidenhain's iron hematoxylin.

Since they are never met with in smears from the bone-marrow, nor in human or animal embryos, Naegeli is probably right in regarding them as pathological phenomena appearing during karyolysis in regenerative cells in the blood. They are, in my opinion, remains of the nuclear membrane. Their clinical significance, if they have any, is not yet understood.

(5) *Red Granules, Red Filaments, etc., Stainable in Erythrocytes with Methylene-Azure-and-Eosin Mixtures*

Naegeli first described a bright red, coarse, basophilic granulation brought out by Giemsa's stain in erythrocytes; large numbers of granules appear in a single cell. He found many such cells in the blood of pernicious anemia and in that of anemia pseudoleukemica infantum. This kind of granulation has also been met with in lead poisoning and in other anemias and leukemias. They were early described in this country by Cabot (1903). Like Cabot's ring-bodies, they appear never to be met with in embryonic blood. Naegeli suggests that they may result from the splitting up of Cabot's rings into granules, though other nuclear parts may also contribute to the granulation besides the wall of the nucleus, the part supposed to give rise to Cabot's rings.

Sometimes, fine red spots, or extremely minute filaments, are also seen in red corpuscles. Naegeli observed them in severe lead poisoning, along with abundant blue basophilic granulation, in a case in which normoblasts, Howell's bodies and Cabot's rings were abundant. They have also been seen in pernicious anemia and in other severe forms of anemia, but never in embryonic blood.

(6) *Schüffner's Granules*

These are minute, dark reddish, chromatin-like dots, observed in the red cells in certain forms of malaria. They are revealed best with Romanowsky stains. T. R. Boggs has shown that these granules are by no means identical with ordinary basophil granules.

(7) *Basophilic Granulation of the Red Corpuscles*

While the preceding abnormalities of staining are relatively rare in the blood, the basophilic granulation now to be described is a very common appearance, and is what is meant ordinarily when "basophilic granulation of the red corpuscles" is mentioned. One sees coarser and finer granules, intensely stained with basic dyes, inside the red corpuscles. They are usually round, though sometimes angular, in shape. There may be only a few in the cell, in which case they are prone to be large and multangular, or there may be great numbers of them, in which case the granules are smaller and round. Often, large and small granules occur together in the same corpuscle.

These basophil granules are best seen in simple methylene-blue staining when the granules stain deep dark blue, but they also show up well with the Romanowsky stains (Giemsa's, Wilson's), appearing here also as deep-blue granules.

These granules attained to an especial importance when their constant occurrence in the blood in lead poisoning became known. In this connection, they are often referred to as "Grawitz granules."

There has been much discussion as to whether this basophilic granulation represents a degeneration of the protoplasm, or is a sign of regenera-

tion. Grawitz especially championed the degeneration view, and believed that the occurrence of this basophilic granulation always represents some obscure blood intoxication. Other hematologists just as strongly deny the degenerative significance of basophilic granulation and support the view that we have to deal here with young cells, and that the occurrence of basophilic granulation runs more or less parallel with the occurrence of erythroblasts in the blood, the latter being an undoubted sign of regenerative activity of the bone-marrow.

Basophilic granulation has been met with in every variety of anemia, but it may be absent also in a given case of any form of anemia, a fact which, as Naegeli points out, indicates that the change cannot be due to the anemia itself, but must depend upon definite biological conditions frequently accompanying anemia.

As has already been said, this basophilic granulation is most pronounced in lead poisoning, as was first recognized by Behrend (1899). It is especially marked when there is much anemia accompanying the poisoning; but the degree of granulation does not go parallel to that of the intoxication; the number of basophilic cells may vary greatly from day to day.

In embryonic red corpuscles (animal and human), some basophilic red cells are always present at certain stages, and they are more numerous in the bone-marrow than in the circulating blood. They are met with sometimes in adult red marrow, though in small numbers. It is interesting that, in aplastic anemia, the blood may be free from basophilic red cells, even when they are present in considerable numbers in the marrow (Naegeli; Carslaw and Dunn).

The granules are never present in parts of a red corpuscle free from hemoglobin. They are invisible in ultra-violet light.

As to the actual genesis of the basophilic granulation within the corpuscle, there is still much dispute. Some believe that they are derived from the nuclear substances; others regard them as originating in the protoplasm itself, especially as, in Giemsa's stain, these granules are blue, while nuclear derivatives are red, but it should be remembered that pyknotic nuclei stain blue in Giemsa's stain.

The close relation of the granules to polychromasia is certainly striking to every worker, and in my laboratories it has been common to speak of the basophilic granulation as *punctate polychromasia,* and of ordinary polychromatophilic protoplasm as *diffuse polychromasia.*

For a full discussion of the different views regarding these abnormal appearances in the red corpuscles, the reader is referred to the careful descriptions in C. P. Emerson's *Clinical Diagnosis,* and to that "mine" of hematological observations, O. Naegeli's *Blutkrankheiten und Blutdiagnostik.*

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8. The White Blood-Cells in Dried and Stained Smears

Under normal conditions certain definite varieties of leukocytes only, are to be found in the blood. With practice, most of these may be recognized in fresh preparations, as has already been pointed out, but for exact studies of them, and for making differential counts, we rely upon suitably stained smears.

The practice of differential counting has for its aims, (1) the determination of the percentage relations of the various leukocytes to one another, and (2) the determination of their absolute number per c. mm. of blood by applying the percentages thus found to the total count of the white corpuscles made from the blood at the same time, by the hemocytometer. (See below, Enumeration of the Different Varieties of White Blood Corpuscles in Stained Smears).

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(*a*) *Ehrlich's Classification of the Normal White Blood-Cells*

The white cells of normal blood may be conveniently divided into six groups: (i) polymorphonuclear neutrophils (P. M. N.); (ii) polymorphonuclear eosinophils (P. M. E.); (iii) polymorphonuclear basophils (P. M. B.); (iv) small mononuclears (S. M.) or lymphocytes (L.); (v) large mononuclears (L. M.); and (vi) transitionals (T.).

i. Polymorphonuclear Neutrophils (P.M.N.)

These are the most numerous; they make up, on the average, between 60 per cent and 70 per cent of the total number of white corpuscles of normal blood, *i. e.*, in absolute numbers they amount to from 4,000 to 5,000 per c. mm.

The cells are 9-12 μ in diameter. The *nucleus* presents variable forms; it may be rod-shaped, tortuous, S-shaped, or V-shaped; or it may appear to be divided into several segments, or lobes, though these are, in reality, always connected by delicate chromatin threads. Ultra-violet light passes through the nucleus of a P. M. N. more readily than through the nucleus of a lymphocyte (Grawitz). The nuclei stain intensely in basic dyes; on close examination, one can see, besides the deeply stained basic chromatin, the unstained transparent lacunae of oxychromatin, the latter being more abundant in the interior than at the periphery of the nucleus. There are no nucleoli.

The *protoplasm* is relatively abundant, is usually slightly oxyphil, though in young forms slightly basophil, and is thickly studded with minute, even-sized, neutrophilic granules (ϵ-granules of Ehrlich); these granules have not exactly the same affinities for acid and basic dyes—they are not quite "neutrophil;" for the acidophil tendency preponderates to a slight degree in the older cells, and the basophil tendency in the younger.

These neutrophilic cells are the common pus cells; they are actively phagocytic elements. They are of myeloid origin, being derived from n-myelocytes (*q. v.*). They contain leukoprotease (proteolysis, autolysis), peroxidase (bluing guaiac tincture), and phenolase (synthesis of indophenol blue). They may be responsible for the carriage of antitoxic and bactericidal substances, though these also occur free in the serum. They also contain iodophilic substances, especially when suppuration is going on in the body.

Summary of Staining Features of P. M. N.

In Ehrlich's Triple Stain.—(1) Nuclei, dark green, or blue, often with black, jagged granules lying upon them; these granules are the perinuclear granules of Neusser, now known to be artefacts (precipitates). (2) Protoplasm, thickly studded with extremely minute lilac, or reddish-violet, granules.

In Jenner's Stain.—(1) Nuclei, dark blue, oxychromatin shows well.

(2) Protoplasm, granules pink or violet; younger granules pinker, older granules bluer.

In Wilson's or Giemsa's Stain.—(1) Nuclei, dark reddish purple, oxychromatin often visible. (2) Protoplasm, granules poorly differentiated, often unevenly stained, red to violet-red, or lilac.

ii. Polymorphonuclear Eosinophils (P.M.E.)

These make up from 2 per cent to 4 per cent of the white corpuscles of normal blood, *i. e.*, in absolute numbers, 150-300 per c.mm. They are usually a little larger than the P. M. N., and are easily distinguishable from them by their nuclei and, especially, by the large size of their granules, and the staining behavior of the latter.

The *nucleus* is somewhat simpler (less segmented, plumper, the parts more rounded, than in the preceding variety), and the basochromatin is less abundant, staining more feebly. There are no nucleoli.

The *protoplasm* can scarcely be seen on account of the granules; in simple methylene-blue staining it is seen to contain a delicate basophil reticulum. It contains very large acidophil granules, easily recognizable, as we have already seen, in unstained preparations by their strong refraction. I believe that I was the first microchemically to demonstrate that these granules contain iron (ammonium-sulphid reaction), an observation subsequently confirmed by Russian workers. The granules stain well in acid dyes, best of all in Jenner's stain.

The P. M. E. arise from the e-myelocytes of the bone-marrow.

Summary of Staining Features of P. M. E.:

In Ehrlich's Triple Stain.—(1)Nucleus, pale blue, undifferentiated, often with black perinuclear granules of precipitate. (2) Protoplasm, filled with large brilliant red granules, or (with Morris's mode of preparing the stain) with brick-red, or copper-colored, granules.

In Jenner's Stain.—(1) Nucleus, pale blue. (2) Protoplasm, closely crowded with exquisitely differentiated, brilliant red, granules.

In Wilson's, or in Giemsa's Stain.—(1) Nucleus, reddish-purple. (2) Protoplasm, granules poorly stained, pink, red, yellow, or purplish-brown—rather disappointing.

iii. Polymorphonuclear Basophils (P.M.B.) or "Mast-cells" (Ma.)

These average 8-10 μ in diameter; they are thus relatively small leukocytes. The mast-cells make up about one-half per cent of the white corpuscles of normal blood; in absolute numbers, from 40 to 50 cells per c.mm.

The *nucleus* is very different from that of the neutrophils and from that of the eosinophils; it has a polymorphism of its own kind, reminding me somewhat of the nucleus of a small megakaryocyte of the marrow; it stains feebly owing to its relatively small content of basichromatin, and it is somewhat obscured by the deeply stained granules that lie above it. There

are no nucleoli. In the *protoplasm* are contained coarse, basophilic, granules, which, in unstained preparations, are not refractive; these granules are easily soluble in water, so that, with some kinds of fixation, they dissolve out, leaving vacuole-like spaces. The staining of the granules in the ordinary stains, though basophil, is also somewhat metachromatic.

The mast-cells of the blood contain phenolase and peroxidase, differing in this respect from the mast-cells of the fixed tissues (Pappenheim).

The idea formerly held that these basophilic leukocytes are degeneration-forms has been given up. They are normal blood cells, and arise from the b-myelocytes of the bone-marrow, not from lymphocytes. In leukemia, very much larger forms of mast-cells appear in the blood, often in considerable numbers (*q. v.*).

Summary of Staining Features of the P. M. B. (or Mast-cells).

In Ehrlich's Triple Stain.—(1) Nucleus, bluish-green. (2) Protoplasm, strikingly white, usually free from granules, the former sites of these being sometimes represented by "vacuoles"; very "resistant" granules may be present, stained almost black.

In Jenner's Stain.—(1) Nucleus, pale blue. (2) Protoplasm, filled with coarse violet-lilac, or purple, granules; granules well preserved, owing to absolute-methyl-alcohol fixation. This is probably the best clinical staining-method for the demonstration of these granules.

In Wilson's, or in Giemsa's, Stain.—(1) Nucleus, reddish-purple, well-differentiated (if not over-stained), showing the typical, peculiar, form. (2) Protoplasm, sometimes contain well-preserved granules, stained reddish-purple; sometimes, the granules are dissolved out, leaving vacuole-like spaces, in which event the protoplasm is mauve-colored in Giemsa's stain.

In Simple Dahlia.—Granules violet.

iv. Small Mononuclears (S.M.) or Lymphocytes (L.)

These cells are about the size of normal erythrocytes (7-9 μ in diameter), and contain a relatively large, deeply staining, round or oval, often somewhat indented, nucleus, which nearly fills the cell; the nucleus is surrounded by only a narrow rim of slightly basophil protoplasm. Under normal conditions, they make up from 20 to 25 per cent of the white blood-cells, in absolute numbers, 1,500-2,000 per c.mm. In sucklings, they make up 50 per cent of the total white count (Benjamin); in childhood, up to the 10th year, the lymphocytes average between 40 per cent and 60 per cent of the total white count (Naegeli).

The *nucleus* of the lymphocyte has a strong affinity for basic dyes, being poor in oxychromatin. A compact nuclear framework, not unlike the "wheel-spoke" arrangement of the nucleus of the normoblast, can often be made out. Every lymphocyte contains one or two oval nucleoli, each with a distinct limiting-membrane. In smears stained by Wilson's, or by Giemsa's, stain, the blue nucleolus may help, in differential counts, to identify the cell as a lymphocyte (Naegeli).

The *protoplasm* of the lymphocyte, when unstained, looks granular both on ordinary microscopic examination, and on "dark-field" examination; but by most staining methods (except those of Romanowsky and of Schridde), no granules appear.

There is a slight basophilic intra-protoplasmic network, least marked near the nucleus; this accounts for the clear perinuclear zone so often seen in the lymphocytes in stained smears.

With Wilson's, or with Giemsa's, stain, about $\frac{1}{3}$ of the lymphocytes (not more) contain a few red granules (some fine, some coarse); these are the so-called *azure granules* (Michaelis and Wolff). According to Naegeli, such azure granules occur only in cells of lymphadenoid origin; they are never present in cells of myeloid origin (myeloblasts), nor in the large mononuclear or transitional forms; if this be confirmed, it will be a helpful method of distinguishing lymphocytes from the cells that sometimes resemble them very closely.

The lymphocytes of the chronic lymphatic leukemias do not contain azure granules; but the large pathological lymphocytes of certain acute lymphatic leukemias almost all contain abundant azure granules. (See the beautiful Plate 17 in Naegeli's treatise.)

The lymphocytes also contain a small number of short, rodlike perinuclear *fuchsinophil granules* (Schridde) in specimens stained by the Altmann-Schridde method; similar fuchsinophil structures occur in myeloblasts and in transitional forms, but it is said that in their shape, number and distribution the latter differ from the lymphocytic structures. These fuchsinophil structures of the lymphocytes are doubtless mitochondria. Schridde's fixation is not the best for mitochondria. The studies of mitochondria by E. V. Cowdry, who uses R. R. Bensley's methods of fixation and staining, make it seem desirable that the whole matter of mitochondria in lymphocytes, myeloblasts, etc., be restudied by these better methods.

In children, and in pathological bloods, a larger lymphocyte (lymphoblast) (12-15 μ in diameter) occurs; it differs in no way except in its size from the ordinary small lymphocyte; it seems to correspond to the cells of the germinal centers of the lymph glands.

Lymphocytes never contain neutrophil, eosinophil or basophil granules. There is no evidence that they contain leukoprotease, phenolase, or peroxidase. The lymphocytes are of lymphadenoid origin (lymph glands, malpighian follicles of spleen, lymph nodules of organs). They do not arise from leukopoietic tissue of the bone-marrow proper, though probably a few arise from the minute lymph nodules that occur there as well as in other organs.

The cells that resemble lymphocytes and which occur in the bone-marrow in great numbers (myeloblasts of Naegeli), are, in reality, entirely different cells. (For pathological lymphocytes, Rieder's forms, etc., see below).

Summary of Staining Features of S. M. or L.:

In Ehrlich's Triple Stain.—(1) Nucleus, bluish-green, undifferentiated; black dots (ppt.). (2) Protoplasm, a small rim, pale, or feebly rose-colored, often with a clear perinuclear ring, as though the nucleus had shrunk away from the protoplasm. No granules.

In Jenner's Stain.—(1) Nucleus, dark blue. (2) Protoplasm, pale blue, perinuclear lighter zone. No granules.

In Wilson's and in Giemsa's Stain.—(1) Nucleus, beautiful dark reddish-purple; the indentation is well shown, but not quite so well as in hematoxylin preparations; in broken or squeezed lymphocytes, a single blue nucleolus may be visible. (2) Protoplasm, light blue; perinuclear paler area; in 1/3 of the cells a few red azure granules.

In Carbol-pyronin Methyl Green Stain.—(1) Nucleus, blue; nucleoli, red. (2) Protoplasm, deep, brilliant red.

In differential counts made with Wilson's stain, some of our best clinicians adopt the rule that mononuclear cells smaller than the average-sized polymorphonuclear neutrophil (10 μ) shall be classed as small mononuclears (lymphocytes), and that mononuclear cells larger than this shall be classed as large mononuclears and transitionals. In normal blood, such a rule will lead to a count in close agreement with counts based upon the specific morphological and tinctorial characters of lymphocytes, but in young children and in various pathological states where large lymphocytes occur, a count made according to this rule could, it seems to me, be misleading.

v. Large Mononuclears (L.M.)

These and the next type, the transitionals, belong in reality together, as the transitionals are probably older forms of the large mononuclears, differing from them in size, in nuclear form, and in case of differentiation of the granules. Still, for didactic reasons, it is convenient to treat the two forms separately.

The large mononuclears and transitionals are large white cells (12-20 μ), and always, in contrast with lymphocytes, show a relatively abundant protoplasm. They are easily broken up, and in smears are often so found. The L. M., without the transitionals, make up about 6-8 per cent of the normal white count, in absolute numbers, 400 to 600 per c.mm.

The *nucleus* is large, round or oval, often slightly indented, poor in basichromatin and, therefore, it stains feebly by all methods. It resembles closely the nucleus of a myelocyte. No nucleoli are visible in the nuclei in smears treated with the usual blood-stains, but, on "vital" staining, each nucleus is seen to contain 3-4 nucleoli.

The *protoplasm* contains a delicate network (feebly basophil in simple methylene blue or in hematoxylin staining), but there is no special perinuclear pallor, thus differing from the protoplasm of the lymphocyte. In unstained blood, extremely minute granules are seen to fill the protoplasm, but on staining smears no granules, or very few, are seen by the usual methods, except that (1) in Ehrlich's triple stain, a few lilac granules may be seen, especially in the transitionals (hence the name given to these by

Ehrlich, who, erroneously, thought them to be stages intermediate between large mononuclears and polymorphonuclear neutrophils), and (2) in Jenner's stain, a few, single, small, sharply differentiated, red granules can here and there be seen. But, as Naegeli has demonstrated, extremely minute stainable granules are present in enormous numbers in every one of these cells, and can be brought out by especially careful Giemsa staining. In ordinary Giemsa smears, stained briefly, only a few red granules appear, but longer staining of well-spread smears with a perfect Giemsa staining reveals a very large number of fine granules distributed generally throughout the protoplasm, most abundant at the periphery, but also abundant everywhere throughout the protoplasm of the cell, even close to the nucleus. Of 100 large mononuclears and transitionals studied in one case, Naegeli found 87 very closely crowded with granules, 13 showing abundant granules, none scantily granular, and none devoid of granules.

It seems probable to me that we are dealing here with a granulation *sui generis*—best designated as the "mono-granulation"; no white blood-cell, other than the large mononuclear and the transitional, contains this granulation.

There has been much dispute as to the nature of these granules. They are certainly different from the azurophil granules of lymphocytes and from the neutrophil granules of the polymorphonuclear leukocytes, though they resemble the latter more closely than they do the former. The "mono-granulation" is regarded as azurophil by some (Pappenheim, Hirschfeld, Ferrata), as neutrophil by others (Cabot, Naegeli, Eric Meyer, Schleip, Ziegler), and as a mixture of azurophil and neutrophil by others (Türk, Benjamin).

The large mononuclears contain phenolase, as the indophenol-blue synthesis is positive; this is in striking contrast with the behavior of the lymphocytes, which never contain phenolase. The L.M. also yield positive peroxidase-reactions.

The origin of the large mononuclears and transitionals has also been much disputed. It seems to me probable that Naegeli, Rieux, and Ziegler are right in regarding them as myeloid in origin. It has been held by others that they come (1) from the lymph glands (Benda, Weidenreich, Pappenheim), (2) from the spleen-pulp cells and lymph-cord cells of the lymph glands (Meyer and Heineke, Türk), (3) from the endothelial cells of the vessels (Weidenreich), or (4) from adventitia cells (Sternberg, Helly); but the arguments in favor of these views seem to me to be defective. In favor of a myeloid origin are (1) the form and structure of the nucleus, (2) the presence of phenolase, and of peroxidase, (3) the character and distribution of the granules, and (4) especially, the behavior of the cells in pathological states (*increase* when myeloid leukopoiesis is stimulated, also when the spleen is removed, and when the lymphadenoid tissue of the body has undergone extensive destruction; *decrease* when myeloid leukopoiesis is depressed, as in long-continued severe hemolytic anemias, in aplastic anemias, and in the lymphadenoses). One difficulty in determining their origin is the impossibility, as yet, of staining the mono-granulation in histological sections.

Summary of Staining Features:

In Ehrlich's Triple Stain.—(1) Nucleus, very pale blue. (2) Protoplasm, abundant, pale rose, with or without fine reddish-lilac granules.

In Jenner's Stain.—(1) Nuclei, dark blue. (2) Protoplasm, blue network, sometimes a few red granules.

In Giemsa's Stain.

(a) *Brief Stain.*—(1) Nuclei, reddish-purple, well differentiated. (2) Protoplasm, a few red granules.

(b) *Longer Stain.*—(1) Nuclei, overstained. (2) Protoplasm, thickly studded with fine lilac granules from periphery to nucleus.

If the rule of some be adopted that mononuclears above 10 μ in diameter be grouped, in differential counts, with the L. M., then this group will include, besides the true L. M., a few cells of the true lymphocytic type (S. M.), the size of, or larger than, an average P. M. N. The argument of those who follow this rule is that while they clearly recognize the non-identity of these two cell types (large lymphocytes and large mononuclears), the practice of separating these two groups in making differential counts is of theoretical, rather than of practical, advantage. Personally, I cannot help but feel, that it is better sharply to distinguish between true lymphocytes and true large mononuclears in making differential counts, especially in any unusual case.

vi. Transitionals (T.)

These are the largest cells encountered in normal blood; they have deeply notched, or "saddle-bag" nuclei, staining somewhat more deeply than the nuclei of the large mononuclears, but still feebly and like them surrounded by an abundant, slightly basophil, protoplasm. They contain more granules than the L. M., some of the granules staining lilac with Ehrlich's triple stain. In other respects, what has been said for the L. M. above, holds also for these "transitionals."

They were called transitionals because Ehrlich thought them, erroneously, to be forms intermediate between L. M. and P. M. N. We now believe them to be the maturer derivative of L. M.; they do not become transformed into polymorphonuclear neutrophils.

They are often much increased in Hodgkin's disease (*q. v.*). Normally, they make up between 2 and 3 per cent of the total count of the white cells, in absolute numbers, 150-225 per c.mm.

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(b) White Cells Not Appearing in the Blood Except in Pathological States

Under pathological conditions, several varieties of white blood-cells, not present in normal blood, may appear in the circulating blood and be recognizable on microscopic examination. They include the following:

i. **Cells of Myeloid Origin.**

(1) Myelocytes (M.):
  (a) Neutrophilic myelocytes (n-M.)
  (b) Eosinophilic myelocytes (e-M.)
  (c) Basophylic myelocytes (b-M.), or Mast-myelocytes.
(2) Myeloblasts (Mb.):
  (a) Ordinary normal bone-marrow type (o-Mb.)
  (b) Pathological type (p-Mb.) (Türk's "irritation-form").
(3) Bone-marrow giant cells or megakaryocytes (Mg.)

ii. **Cells of Lymphadenoid Origin.**

(1) Lymphoblasts (Lb.):
  (a) Ordinary germinal center type (o-Lb.)
  (b) Pathological type (p-Lb.) (Rieder's form).
(2) Plasma cells (Pl.)

i. Cells of Myeloid Origin

(1) *Myelocytes* (*M.*)

These cells are the predominant cells in the normal bone-marrow. Normally, they are never present in the blood, but they do go over into it in a number of pathological states, especially in myeloid leukemia, when they may be present in the blood in enormous numbers. These myelocytes are large cells (15-20 μ).

The *nucleus* stains feebly; it is eccentric, round or oval, and is sometimes indented; there are no nucleoli visible with some of the stains, but very beautiful nucleoli may be seen in smears stained with Giemsa's stain or with carbol-pyronin methyl green. The pallor of the stained nucleus is due to poverty in chromatin (so-called leptochromatic nucleus).

The *protoplasm* is usually abundant, often broader on one side of the nucleus than on the other, is slightly basophil, and is studded with granules (neutrophilic, eosinophilic or basophilic).

(a) **Neutrophilic Myelocytes (n-M.)**.—The n-myelocytes are the predominating cells in the marrow and are the form of myelocyte that enters the blood in largest numbers in pathological states. Some of the granules are a little more basophil than others, so that the granules may look somewhat unevenly stained.

The n-M. arise from the myeloblasts of the bone-marrow.

(b) **Eosinophilic Myelocytes (e-M.)**.—The e-myelocytes are not infrequently seen in the blood in myeloid leukemia; they may occur in the blood in smaller numbers in outspoken eosinophilic leukocytoses.

Most of the granules stain like ordinary eosinophil granules, but on

account of their youth, some of them contain a basophil component so that, in the same cell, different colored granules may be visible.

The e-M. arise from the myeloblasts of the marrow.

(c) **Basophilic Myelocytes (b-M.).**—The b-myelocytes, or mast-cell myelocytes, are always small. The granules are more resistant to water than those of the polymorphonuclear basophils. They may contain immature, as well as mature, granules.

These b-M. also have their origin in the myeloblasts of the marrow.

When myelocytes are in the blood, one may also sometimes see forms transitional between the myelocytes and the polymorphonuclear leukocytes. These are the so-called *meta-myelocytes*. The nucleus shows a beginning segmentation, the cell is smaller, the nucleus richer in basichromatin.

Transition forms between the myeloblasts and the myelocytes may also enter the blood—so-called *pro-myelocytes*. The nucleus is large and poorer in chromatin; nucleoli are distinctly demonstrable; a strongly basophilic protoplasmic network can be seen, and single immature granules are present. The neutrophilic pro-myelocytes contain immature neutrophilic granules, which stain violet in methylene blue, but are so fine that they are easily distinguishable from the granules of mast-cells. According to Naegeli, these are young neutrophil granules, not, as Pappenheim maintains, azure granules.

Summary of Staining Behavior of Myelocytes:

In Ehrlich's Triple Stain.—(1) Nucleus, pale blue. (2) Protoplasm of the n-myelocytes closely studded with minute lilac granules, of the e-myelocytes with red or yellow granules, of the b-myelocytes with vacuoles.

In Giemsa's Stain.—(1) Nucleus, reddish-purple; peculiar network or striation; often blue nucleoli. (2) Protoplasm markedly basophilic in the younger forms, less basophilic in the older forms; granules in the n-myelocytes, dark reddish-violet, not nearly so well differentiated as in Ehrlich's stain; in the e-myelocytes, the granules may be blue, or red; in the b-myelocytes, large, widely separated, blue granules, often mixed with mauve granules in the more mature forms.

(2) *Myeloblasts* (*Mb.*)

These are the non-granular cells of the marrow, which are believed to be the mother-cells of the granular myelocytes. Clinicians owe a great debt to O. Naegeli, of Zurich, for having established the independence and the exact position of the myeloblasts. Formerly, they were confused with large lymphocytes, but now we can feel very sure that these cells are entirely different from lymphocytes, and that they are always of myeloid, never of lymphadenoid, origin.

They are the dominant cells in the embryonic myeloid tissue, and they are quite numerous in the normal bone-marrow of children, though in adults the bone-marrow cells consist chiefly of granular myelocytes. In the bone-marrow in the anemias and in the leukemias, however, myeloblasts are more abundant.

Myeloblasts sometimes go over into the blood; they do so in especially large numbers in the acute myeloid leukemias; a few may be seen in the blood in the more chronic myeloid leukemias. They are then found in companionship with granular myelocytes.

The myeloblasts are large cells (12-20 μ), though small forms do occur (micro-myeloblasts), and it is these that are most often confused, nowadays, with large lymphocytes.

The *nucleus* is round or oval and resembles that of the myelocytes, having a fine, feebly-staining (leptochromatic) framework. There are from 2 to 6 nucleoli, easily stainable in Wilson's stain, and on vital staining, but these exhibit no distinct nucleolar wall.

The *protoplasm* contains a fine basophilic reticulum, which, in contrast with that of the lymphocyte, extends right up to the nuclear margin, not leaving any clear perinuclear area. In young myeloblasts, no granules can be demonstrated by the ordinary methods, though in transition forms to myelocytes (the so-called pro-myelocytes) a few immature granules are demonstrable.

By Schridde's method, fuchsinophil structures are demonstrable in the myeloblasts, but they differ in form and distribution from those of the lymphocytes. These structures should be studied by Bensley's methods, as applied by Cowdry.

The myeloblasts may contain the proteolytic ferments, as well as phenolase and peroxidase; lymphocytes do not contain these ferments.

According to Naegeli, the distinguishing characters of the myeloblasts, as compared with the lymphocytes, are the following:

(1) Morphological differences.
  (a) Nuclear structure different.
  (b) Constant absence of true perinuclear clear area.
  (c) Constant absence of genuine azure granules.
  (d) Differences in number and structure of nucleoli.
(2) Biological differences.
  (a) Presence of proteolytic ferments.
  (b) Presence of phenolase and peroxidase (indophenol-blue synthesis; positive guaiac reaction).
  (c) Definite proof of transition forms between myeloblasts and myelocytes.
  (d) Occurrence, along with erythroblasts, in hematopoietic foci.
(3) Histological differences.
  (a) Absent from lymphatic organs, especially from the lymph follicles and the germinal centers.
  (b) Always found in loose tissue, along with other myeloid cells, and not in follicles.

Two types of myeloblasts may enter the blood in the pathological states:

(1) The ordinary bone-marrow type, often occurring in very large numbers, and

(2) The "pathological" type, asserted by Naegeli to be identical with

Türk's irritation forms; when present, they occur singly, or in small numbers.

(a) **Ordinary Type of Myeloblast (o-Mb.).**—This corresponds to the general description of myeloblasts given above.

Summary of Staining Features:

In Ehrlich's Triple Stain.—(1) Nucleus, feebly stained, undifferentiated, like the myelocyte nucleus. (2) Protoplasm, rose-colored, or pink.

In Wilson's Stain (*or Giemsa's*).—(1) Nucleus, reddish-purple with fine reticular network or striation; blue nucleoli, with no distinct nucleolar wall. (2) Protoplasm, deep blue; no perinuclear clear area; no granules; in the small myeloblasts (micro-myeloblasts) there may be a narrow rim of protoplasm, much like that in lymphocytes, but some protoplasm can always be seen outside of every part of the nucleus (Klein). A cell containing azure granules is never a myeloblast (Naegeli).

(b) **Pathological Myeloblasts (p-Mb.) (Türk's "Irritation Form").**—These cells are now thought to be myeloblasts. They are as a rule large cells.

The *nucleus* is round or oval, and shows a delicate chromatin network (lepto-chromatic nucleus), and several nucleoli, though these cannot be distinctly seen in Wilson stainings.

The *protoplasm* is relatively abundant, strongly basophil, and nearly always definitely vacuolated; it never contains granules. In smears stained by Wilson's or Giemsa's method, the protoplasm is of a deep ultramarine-blue color, and a similar appearance is seen with Jenner's stain. These "irritation forms," or pathological myeloblasts, have been met with in the blood in various infectious diseases, especially in croupous pneumonia (Türk), in encephalitis, and in acute fat-necrosis with a high grade of leukocytosis (Naegeli), in German measles (Hildebrandt), in lead poisoning, in acute myeloid leukemia, and in many anemias, especially in severe anemias of the Addison-Biermer type They have also been met with in some of the anemias of children. These cells do not occur in normal blood.

Summary of Staining Behavior of p-Mb.

In Ehrlich's Triple Stain.—(1) Nucleus, pale blue. (2) Protoplasm, intense reddish-brown.

In Wilson's or in Giemsa's Stain.—(1) Nucleus, reddish-purple; nucleoli not distinctly visible. (2) Protoplasm, deep, ultramarine blue, usually with distinct vacuoles; no granules, and, especially, no azure granules, present.

In Hematoxylin and Eosin.—(1) Nucleus, pale purple, or lilac, with several pale nucleoli; nucleus larger and much paler than that of lymphocytic plasma cells. (2) Protoplasm, very pale purple, with vacuoles; no distinct perinuclear clear area.

In Carbol-pyronin Methyl Green.—(1) Nucleus, eccentric, violet, less blue than that of a lymphocyte in the same stain; red nucleoli sometimes visible. (2) Protoplasm, more abundant than that of a lymphocyte, deep red and vacuolated.

(3) *Bone-Marrow Giant-Cells or Megakaryocytes (Mg.)*

The megakaryocytes (Howell) of the bone-marrow, which give rise to the blood platelets (J. H. Wright), are ordinarily, enormous cells with large, hollow, convoluted nuclei, numerous nucleoli, and colonies of centrosomes (Heidenhain). A few of the smaller ones occasionally get over into the blood; they are quickly filtered out of the circulating blood by the capillaries of the organs (lungs, liver, spleen).

Summary of Staining Behavior:

In Ehrlich's Triple Stain.—(1) Nucleus, greenish-blue. (2) Protoplasm, rose-colored.

In Wilson's, or Giemsa's, Stain.—(1) Nucleus, reddish-purple; nucleoli not distinctly seen. (2) Protoplasm, blue, containing islands, or perinuclear areas, of very fine, and rather indistinct, pink or red granules. The periphery of the protoplasm is usually free from granules.

ii. Cells of Lymphadenoid Origin

(1) *Lymphoblasts (Lb.)*

These are sometimes known as "pathological" lymphocytes. Two forms are met with in the blood.

(a) **Ordinary or Germinal-Center Type of Lymphoblast (o-Lb.).**—Ordinary lymphoblasts (o-Lb.) or large lymphocytes correspond to the normal cells of the germinal centers; these are not infrequently seen in the normal blood of children, and they are occasionally met with in adults under pathological conditions. They stain like normal lymphocytes, differing from them only in their larger size and (slightly) more abundant protoplasm.

(b) **Pathological Type of Lymphoblasts (p-Lb.) (Rieder's Forms).**—These are the giant lymphocytes, and include those with lobulate and tripartite nuclei—the so-called "Rieder forms."

Their *nuclei* stain very badly in Ehrlich's triple stain, and in Jenner's stain. In methylene azure and eosin (Wilson's or Giemsa's stain) the nuclei stain more deeply. The protoplasm is relatively scanty. In places, the nucleus is at the edge of the cell. The *protoplasm* contains a basophil reticulum, often with a definite perinuclear clear area, and is sometimes vacuolated. Azure granules are sometimes present, occasionally in large numbers in the protoplasm.

These cells never contain proteolytic ferments, phenolase, or peroxidase.

These pathological types are met with in acute lymphatic leukemia, and in aleukemic lymphadenoses. Occasionally they are seen in chronic lymphatic leukemia, in Basedow's disease, and in various infectious diseases (Naegeli). These cells are very easily injured; in smears, naked nuclei are sometimes seen, and structureless nuclear clumps (Gumprecht's scales).

Summary of Staining Behavior of p-Lb.:

In Ehrlich's Triple Stain.—(1) Nucleus, very pale greenish-blue, sometimes scarcely stained at all. (2) Protoplasm, often unstained, or rose-colored.

In Hematoxylin and Eosin.—(1) Nucleus, pale purple-blue. (2) Protoplasm, blue, with blue nodules of chromatin network; perinuclear clear area.

In Giemsa's Stain.—(1) Nucleus, deeply stained, reddish-purple; coarse chromatin framework. (2) Protoplasm, bluish; often a deep ultramarine blue; vacuolated. In acute lymphatic leukemia, the cells may contain numerous azure granules.

(2) *Plasma Cells (Pl.)*

True plasma cells are only rarely met with in the blood; those that are seen are of lymphadenoid origin. The cells resemble lymphocytes, but they are a little larger, have an eccentric nucleus with a so-called "wheel-spoke" structure and thick chromatin framework. The protoplasm is intensely basophil, and contains numerous vacuoles. There is always a marked perinuclear clear area. Occasionally, azure granules are visible (Naegeli). Such plasma cells are far less common in the blood than are "pathological" myeloblasts (Türk's irritation forms); the latter have been erroneously designated plasma cells, but can be, as a rule, distinguished from them, by the appearance of their nuclear structure.

Summary of Staining Behavior of Pl.:

In Hematoxylin and Eosin.—(1) Nucleus, eccentric, deeply stained, violet-black; the nucleus has a coarser framework than even that of the small lymphocyte. (2) Protoplasm, strongly basophil, lilac, vacuolated; perinuclear clear area, usually present.

In Ehrlich's Triple Stain.—(1) Nucleus, reddish-purple; coarse framework. (2) Protoplasm, light blue, with clear perinuclear area; sometimes vacuoles; occasionally fine azure granules.

11. Enumeration of the Different Varieties of White Blood-Corpuscles in Stained Smears (So-called Differential Count of the Leukocytes)

Fully as important as the count of the total number of white corpuscles, is the determination of the absolute numbers of the different varieties of white cells present in the blood. When the total count is normal, there may still be great deviations from the normal in the relative numbers of the different varieties of white cells present; thus the lymphocytes, the eosinophils, or the neutrophils are often present, respectively, in disproportionately large or small numbers, pointing to pathological states.

Before undertaking a differential count of the white blood-cells, one should make sure that he has (1) a total white count per c.mm. of the same blood, and (2) a faultlessly spread and stained blood film, preferably made by the cover slip rather than the slide method, and *made at the time*

(9) Synoptic Table of Appearances in Stained Blood Smears*

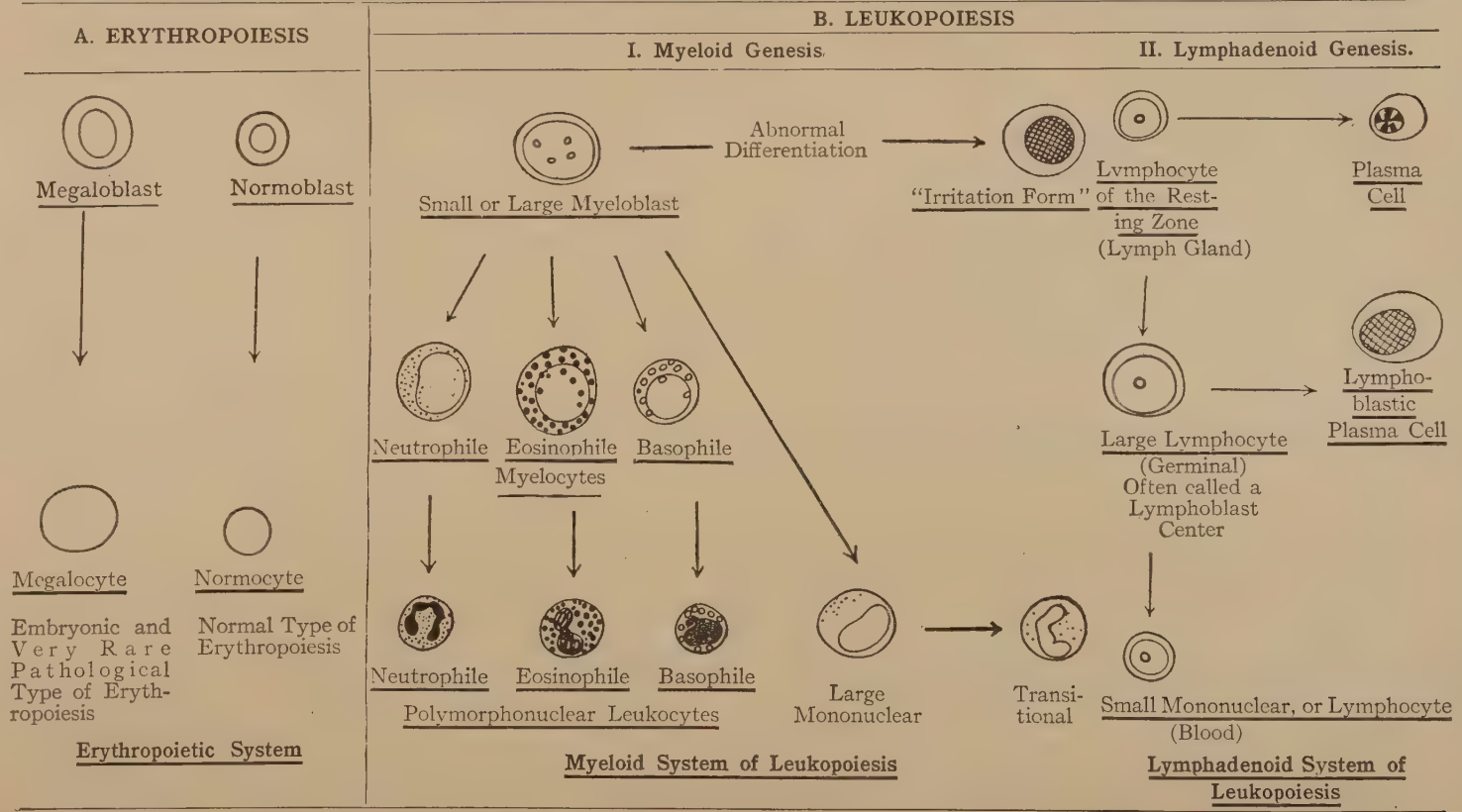
Formed Elements	Ehrlich's Triple Stain	Jenner's Stain	Giemsa's Stain †	Pyronin-Methylgreen
I. Red Blood-Corpuscles				
1. Normal erythrocytes.	1. Buff color; reddish-orange.	1. Pink, or terra-cotta.	1. Pale pink; greyish-pink, or orange-mauve.	1. Grey, or slate color.
2. Polychromasic r. b. c.	2. Reddish-violet; usually not shown.	2 Bluish.	2. Bluish.	2. Red.
3. Howell's bodies.	3. Unstained, or pale green.	3. Blue.	3. Red, or reddish-purple.	3. Blue, green, or red.
4. Cabot's rings.	4. Unstained.	4. Unstained.	4. On long staining, red; sometimes bluish, or purple.	4. Not stained.
5. Basophilic granules.	5. Unstained.	5. Dark blue.	5. Dark blue; in some anemias, often red.	5. Red.
6. Normoblasts.	6. Dark blue-green nucleus.	6. Nucleus, dark blue.	6. Nucleus, reddish-purple, often pyknotic.	6. Nucleus, dark green or blue.
7. Megaloblasts.	7. Pale blue nucleus.	7. Nucleus, paler blue.	7. Nucleus, reddish-purple; large.	7. Nucleus, pale greenish-blue.
II. Normal White Cells				
1. Polymorphonuclear neutrophils.	1. Nucleus, dark greenish-blue; granules, reddish-violet, or lilac.	1. Nucleus, deep blue; ripe granules, small, lilac.	1. Nucleus, dark reddish-purple; granules rose, or reddish-violet, often poorly differentiated.	1. Nucleus, bluish-violet.
2. Polymorphonuclear eosinophils.	2. Nucleus, dark greenish-blue; granules, brick-red, or copper-colored.	2. Nucleus, blue; granules large; brilliant red.	2. Nucleus, as in 1; granules poorly stained, yellow, red, or purplish-brown.	2. As in 1.
3. Polymorphonuclear basophils.	3. Nucleus, dark greenish-blue; granules unstained; vacuoles.	3. Nucleus, blue; granules coarse, violet-blue (metachromatic).	3. Nucleus, as in 1; granules, often dissolved out, if not, reddish-purple; protoplasm mauve; vacuoles.	3. As in 1.
4. Small mononuclears (lymphocytes).	4. Nucleus, pale green; protoplasm, unstained, or feebly rose; no granules.	4. Nucleus, deep blue; protoplasm, blue.	4. Nucleus, deep reddish-purple; protoplasm, pale blue; a few red "azure-granules" in one-third of cells.	4. Nucleus, dark green, or blue; nucleoli, red; protoplasm, brilliant red.
5. Large mononuclears.	5. Nucleus, very pale green; protoplasm, unstained, or feebly rose; no granules.	5. Nucleus, deep blue; protoplasm, paler blue.	5. Nucleus, reddish-purple; protoplasm, pale blue; in well-stained smears, closely studded with extremely minute red-violet granules; these granules often unstained.	5. As in 1.
6. Transitionals.	6. Nucleus and protoplasm as in 5; occasionally, a few lilac granules.	6. Nucleus and protoplasm as in 5; sometimes, a few fine, red granules.	6. As in 5; nuclear form changing; granules constant.	6. As in 1.

Formed Elements	Ehrlich's Triple Stain	Jenner's Stain	Giemsa's Stain †	Pyronin-Methylgreen
III. Pathological White Cells				
1. Neutrophilic myelocytes.	1. Nucleus, pale greenish-blue; granules, fine, reddish-violet, or lilac.	1. Nucleus, blue; granules not very distinct.	1. Nucleus, reddish-purple; nucleoli, blue; protoplasm, blue; fine granules, poorly stained, reddish-violet.	
2. Eosinophilic myelocytes.	2. Nucleus, as in 1; granules brick-red or coppery.	2. Nucleus, blue; granules, red.	2. Nucleus, as in 1; most granules blue, some red.	
3. Basophilic myelocytes.	3. Nucleus, as in 1; granules greenish-black.	3. Nucleus, blue; granules, violet-blue.	3. Nucleus, as in 1; protoplasm, blue; granules, blue, or mauve.	
4. Ordinary myeloblasts.	4. Nucleus, pale greenish-blue; protoplasm, rose; no granules.	4. Nucleus, blue; no granules.	4. Nucleus, reddish-purple; nucleoli, bluish; protoplasm, deep blue.	
5. Pathological myeloblasts (=Türk's irritation form).	5. As in 4; vacuoles.	5. Nucleus, blue; protoplasm, blue, vacuolated.	5. Nucleus, paler reddish-purple; no distinct nucleoli; protoplasm, ultramarine blue, vacuolated; no granules.	5. Protoplasm, brilliant red, vacuolated.
6. Megakaryocytes.	6. Nucleus, greenish-blue.	6. Nucleus, blue.	6. Nucleus, pale reddish-purple; protoplasm, bluish; fine granules, pink.	
7. Plasma-cell lymphoid cells.	7. Nucleus, reddish-purple, coarse framework.	7. Nucleus, blue; protoplasm, blue.	7. Nucleus, eccentric, "wheel-spoke" type, reddish-purple; protoplasm, pale blue, vacuolated, with perinuclear clear area; azurophile granules.	7. Protoplasm, brilliant red.
8. Rieder-cell lymphoblasts.	8. Nucleus, pale greenish-blue.	8. Nucleus, blue; protoplasm, blue.	8. Nucleus, intensely stained reddish-purple, with overlapping parts; protoplasm, blue, perinuclear clear area, often vacuolated, sometimes azurophile granules.	
IV. Blood Platelets.	Poorly stained.	Poorly stained.	Well stained; red center and blue periphery.	Poorly stained.
V. Malarial Parasites.	Poorly stained.	Protoplasm, light blue; chromatin unstained.	Exquisitely stained; protoplasm, light blue; chromatin, red.	

* After R. S. Morris, somewhat modified and extended.

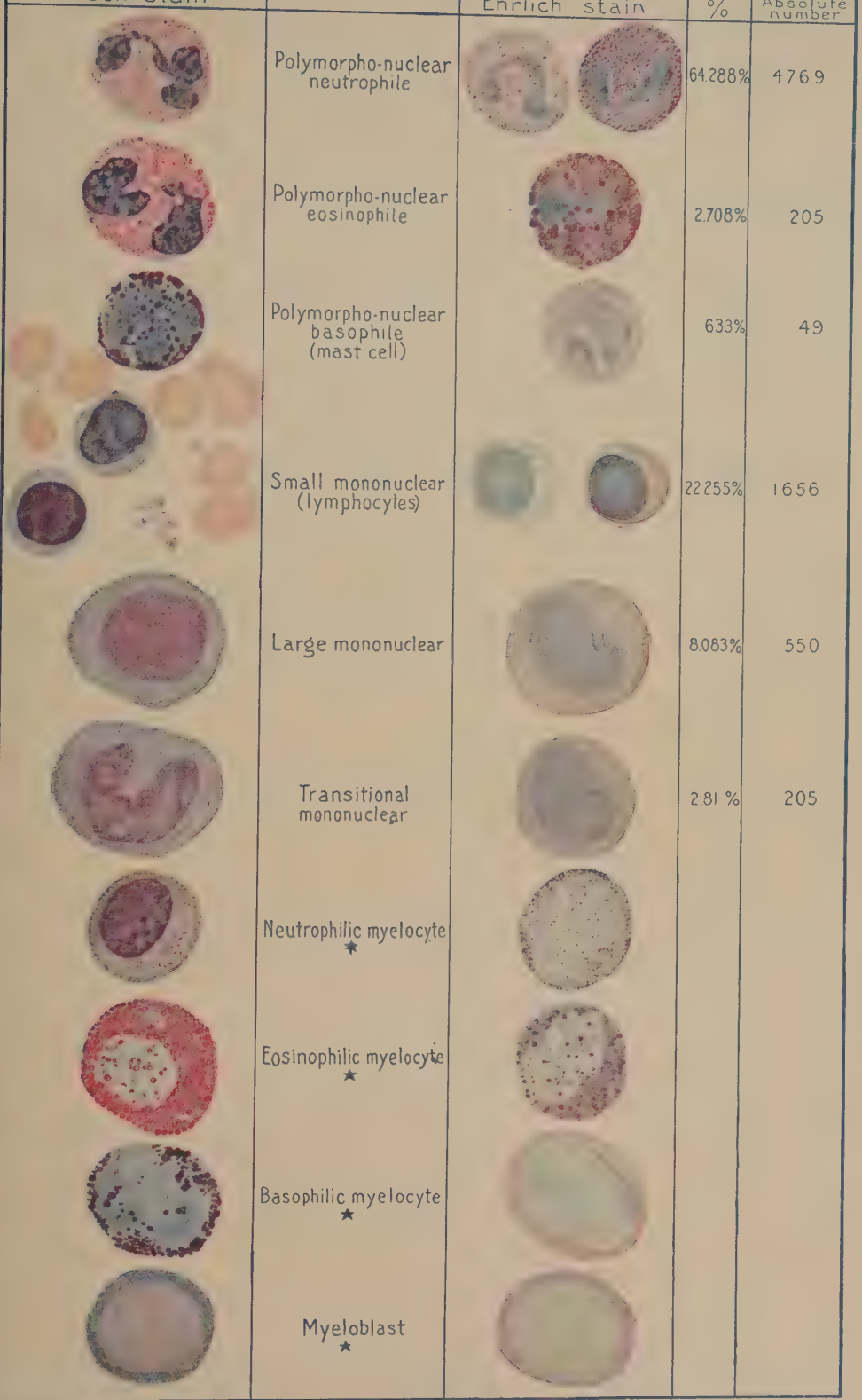
† The group of Romanowsky stains, especially the stains of Wilson, of Hastings and of Wright, yield essentially the same pictures as Giemsa's stain, except that the red cells assume a more pinkish tinge; all nuclear elements are intensely stained with the blue basic dye, being less red than in Giemsa preparations.

(10) Table Illustrating the Origin of the Red and the White Blood-Corpuscles*



*After O. Naegeli, modified.

PLATE XIII



F. Schaefer and D. Pennington fec

★ Cells not present in normal blood

Percentage and absolute number are based on total white count of 7300

White Blood-corpuscles. (Original Drawing.)

the blood is taken for the total count. For routine differential counting, Jenner's stain or one of the modified Romanowsky stains answers every requirement, and for those unpractised in blood work, gives more reliable data than the Ehrlich stain. Differential counts made with the Ehrlich stain, however, should always be used as a check when there are any numbers of unusual cells present. This is particularly necessary for the beginner in order to avoid confusing large mononuclear cells containing many pseudogranules with true myelocytes. (It will be remembered, of course, that the pseudogranulation of the large mononuclear and transitional cells does not stain with the triacid mixture.) As a general rule, the examination of all pathological bloods should be controlled by films stained with the old Ehrlich stain.

To avoid counting the same cells twice, and to make sure that the whole of the smear is carefully gone over, a "mechanical stage" is a necessity. The count should include an analysis of at least 300 cells, and in unusual cases 500, or, better, 1000 cells should be analyzed. Especially, when it is important to determine the exact percentage of the less numerous elements, such as the mast-cells, the plasma cells, or the eosinophile cells, an analysis of less than 500 leukocytes is unreliable. An oil-immersion lens, with Abbé condenser, and a medium strong eye-piece should be employed, as a high magnification is required to resolve the finer of the granulations.

Besides the microscope is placed a sheet of paper, with columns for the different cells, as follows:

DIFFERENTIAL COUNT IN STAINED BLOOD SMEAR. (Total White Count per c.mm. =)

Date: Stain used:

Normal Varieties of White Cells.					
P.M.N.	P.M.E.	P.M.B.	S.M.	L.M.	T.

Erythroblasts		Pathological Varieties of White Cells.						
Normoblasts.	Megaloblasts.	n-M.	e-M.	b-M.	o-Mb.	p-Mb.	o-Lb.	Unclassified. p-Lb. Pl.

As a cell is identified, a stroke is placed in the corresponding column. In case a "smashed" cell is seen it is recorded also. Usually, it can be identified, but now and then one cannot be classified, but it should be kept track of nevertheless, in the extra column, designated "unclassified."

Some hematologists use a square ocular-diaphragm, counting only the cells within this square, as the mechanical stage is moved along.

After a sufficient number of cells have been analyzed, the number in each column is added up and the percentage of each variety in the total number analyzed determined. Then, from the total white count, the absolute number of each variety per c.mm. can be estimated. Thus, for example, in a normal blood, with a total white count of 7,500 cells, the differential count of 500 cells might be as follows:

Varieties of Cells	No. of Cells Counted	Per-centage	Absolute Number per c.mm.
P. M. N. (= Polymorphonuclear Neutrophils)	320	64.2	4815
P. M. E. (= Polymorphonuclear Eosinophils)	14	2.8	210
P. M. B. (Polymorphonuclear Basophils)	3	0.6	45
S. M. (= Lymphocytes) (a) Small. (b) Large.	112	22.4	1680
L. M. (= Large Mononuclears)	40	8.0	600
T. (= Transitionals)	10	2.0	150
n-M. (= Neutrophilic Myelocytes)	...	....	....
e-M. (= Eosinophilic Myelocytes)	...	....	....
b-M. (= Basophilic Myelocytes)	...	....	....
o-Mb. (= Ordinary Myeloblasts)	...	....	....
p-Mb. (= Pathological Myeloblasts)	...	....	....
o-Lb. (= Ordinary Lymphoblasts)	...	....	....
p-Lb. (= Pathological Lymphoblasts and Rieder Forms)	...	....	....
Pl. (= Plasma Cells)	...	....	....
u. (= Unclassified)	1	....	....
Normoblasts	...	....	....
Megaloblasts	...	....	....
Total	500 cells	100%	7500

In some instances, especially where one is following the results of a special kind of therapy, it is desirable to make frequent differential counts and to record the results graphically in the form of "leukocyte curves."

Recent work (Bunting, 1911; S. R. Miller, 1914) has tended to show that the percentage values for the leukocytes of normal blood vary within much wider limits than is commonly taught. This is probably due to a great number of factors, such as climate, altitude, the state of the circulatory system and of digestion, the prevalence of vagotony, etc. It is probable that the normal differential formula differs in various sections of the country; especially in the region of the Great Lakes, the prevalence of general lymphadenoid hyperplasia has been noted, associated with values for the mononuclear elements much higher than are commonly seen elsewhere (Bunting).

A table based upon a recent study by S. R. Miller illustrates very well the variations as observed in a large number of healthy adults in Baltimore. In these differential counts, the rule, to which I have referred, of placing mononuclears up to 10 μ in diameter in the S. M. group, those above 10 μ in diameter in the L. M. group, was followed.

(*a*) *Differential Counts of Normal Blood*

THE GROUP DISTRIBUTION, AVERAGE PER-CENT VALUES, AND ABSOLUTE NUMBERS OF THE LEUKOCYTES, AS DETERMINED IN 650 COUNTS ON 230 NORMAL PERSONS (S. R. MILLER).

P. M. N.		P. M. E.		P. M. B.		S. M.		L. M.		T.	
Percentage Values	No. of Counts	Percentage Values	No. of Counts	Percentage Values	No. of Counts	Percentage Values	No. of Counts	Percentage Values	No. of Counts	Percentage Values	No. of Counts
Over 80%	4	Over 5%	74	Over 1%	137	Over 30%	57	Over 15%	18	Over 4%	79
70–80%	135	4–5%	65	.4–1%	351	25–30%	124	10–15%	101	2–4%	413
60–70%	362	3–4%	72	None	162	20–25%	243	5–10%	359	0–2%	158
50–60%	126	2–3%	207			10–20%	219	Under 5%	172		
40–50%	21	1–2%	125			Under 10%	7				
Under 40%	2	Under 1%	107								
No. of Counts	650		650		650		650		650		650
Total average %	64.2		2.8		.6		22.5		8.0		2.8
Total average No. per c.mm.	4,780		205		49		1,656		550		205

As examples of differential counts in disease contrasted with normal counts the following table will suffice. The figures given for normal blood correspond to the averages found in normal persons in the clinical laboratory for the Johns Hopkins Hospital; the figures given for the several diseases are taken from the table in Seiffert and Müller:

(*b*) *Differential Counts in Some Pathological States*

	Normal.	Chlorosis	Addison-Biermer Type of Anemia	Pneumonia	Chronic Myeloid Leukemia	Chronic Lymphadenoid Leukemia
Red Blood-Corpuscles	5,000,000 = 100%	4,350,000 = 87%	1,200,000 = 24%	4,655,000 = 93%	2,750,000 = 55%	2,500,000 = 50%
Hemoglobin	14 gm. = 100%	56%	37%	90%	50%	35%
Color-Index	100:100 = 1	56:87 = 0.64	37:24 = 1.54	90:93 = 0.97	50:55 = 0.91	35:50 = 0.70
Total white count	7,770	8,700	2,500	19,600	460,000	500,000
Polymorpho-neutrophil	63.5% = 4,900	73% = 6,351	53.5% = 1,337	84.5% = 16,562	33% = 151,800	7% = 35,000
Eosinophils	2.8% = 218	2% = 174	0	0	6% = 27,600	2% = 10,000
Mast-Cells	0.5% = 42	0.5% = 43.5	0	0	10% = 46,000	0
Lymphocytes	22% = 1,725	24% = 2,088	45.2% = 1,130	10% = 1,960	1% = 4,600	90% = 450,000
Large Mononuclears and Transitionals	10.8% = 828	0.5% = 43.5	1.3% = 32.5	5.5% = 1,078	15% = 69,000	1% = 5,000
Neutrophil Myelocytes	0	0	0	0	35% = 161,000	0

(The figures for the normal blood are the averages as determined in the Clinical Lab. J. H. H.—those for the abnormal bloods are taken from Seiffert and Müller.)

(c) *Modifications of Ehrlich's Classification of the Normal White Blood-Cells*

It should be noted here that during the past few years there has been a good deal of criticism of the old classification of the white blood-cells originally advocated by Ehrlich. Notwithstanding the fact that these criticisms and newer suggestions for the classification of leukocytes have come from such recognized authorities as Mallory, Bunting, Warfield, Simon, etc., it has seemed advisable to me to adhere for the present at least to the older and more generally adopted ideas of Ehrlich. The ideas of the classification of white cells, according to the suggestions of Warfield, will be briefly outlined here, however, for the use of those who prefer to follow them in differential counts.

The only point in dispute relates to the non-granular cells, all agreeing with the old classification of Ehrlich as regards the P. M. N., the P. M. E. and the P. M. B.

Instead of the division of the non-granular cells into (1) small mononuclears or lymphocytes, (2) large mononuclears and (3) transitionals, the newer school suggests the division of these cells into (i) lymphocytes, (ii) endotheliocytes and (iii) large mononuclears, described as follows:

(i) Lymphocytes

These vary in size from that of a red cell to that of a P. M. N. They are recognizable by their staining reactions rather than by their size, and exhibit the following characters. The nucleus stains very dark and consists of a very compact chromatin network. The protoplasm is clear, variable in amount, and may contain a few coarse granules.

This group of cells as thus described, therefore, includes (1) the original small lymphocytes of Ehrlich, (2) the larger forms varying in size up to a P. M. N., and (3) a few larger cells with the above staining reactions, which, on account of their size, are usually counted with the large mononuclears in the old classification.

(ii) Endotheliocytes

These include all of Ehrlich's erroneously-named transitionals, and also all of the large mononuclears except those mentioned under lymphocytes, which have the lymphocytic staining reactions and differ from lymphocytes only in size.

These endotheliocytes are the largest cells of normal blood and are characterized by (a) variability in size and shape; (b) a nucleus that is large, variable in shape, being round, kidney-shaped, etc., with loose chromatin network; and (c) a protoplasm that is abundant, reticulated in appearance, and often, apparently, filled with fine granules, which, however, are not true granules, but are really nodes of the reticulated protoplasm. This pseudogranular appearance is common to this entire group of cells.

Endotheliocytes are referred to by some workers as splenocytes.

(iii) Large Mononuclears

These are characterized by being larger than a P. M. N., usually oval in shape, with a very deeply staining round or oval nucleus, which is usually eccentric. The nucleus is much more deeply staining and much more compact than that of

the endotheliocytes. The protoplasm is abundant and stains a very deep blue, almost as deep as the nucleus. These cells correspond to Türk's "irritation forms."

The figures for the normal differential count on this newer basis are given by Warfield as follows:

P. M. N.	50-60 per cent
P. M. E.	2- 8 " "
P. M. B.	4- 2 " "
Lymphocytes, mature (small)	20-30 " "
Lymphocytes, immature (large)	5-10 " "
Endotheliocytes	5- 9 " "
Large mononuclears	0- 2 " "

Pappenheim's Terminology of Pathological White Cells in the Blood.— Very interesting studies of the pathological forms of white corpuscles met with in the blood in the leukemias have been made by Pappenheim of Berlin. His terminology is complex, though in reality easy to understand if one reads his text in association with the excellent figures in his atlas. His *lymphoidocytes* of the marrow correspond to the micro-myeloblasts of the classification used in my descriptions. References are given to the more important of Pappenheim's publications, and they should be read by all active workers in hematology.

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12. Microscopic Examination of the Blood for Parasites, and for Other Foreign Bodies

(*a*) *Animal Parasites*

The animal parasites most frequently found in the blood in the United States are the organisms that cause *malaria* (tertian, quartan, and estivo-autumnal.

The best method of staining the malarial parasites in blood smears is to apply the Giemsa or the Wilson modification of the Romanowsky stain, taking care that all the vessels used, as well as the water employed for dilution, are free from acid. In searching for gametes, the concentration method of Bass and Johns is helpful.

The appearances of the parasites are described in the article on Malaria in the Section on Infectious and Parasitic Diseases; in this section also are described the appearances and methods of demonstrating other animal parasites found in the blood: (1) *Trypanosomes,* (2) larvae of *Filaria bancrofti* (in the blood only at night), (3) larvae of *Filaria loa* (in the blood only in the daytime), (4) larvae of *Filaria perstans* (in the blood both

Fig. 304.—Larvae of Filaria bancrofti in the Blood of Man. (After Railliet, in M. Braun's "Die thierischen Parasiten des Menschen," published by Bale Sons and Danielsson, London.)

day and night), (5) the embryos of *Trichinella spiralis.* In bilharziosis, the parasites of (6) *Schistosomum hematobium,* or (7) *Schistosomum japonicum* live in the blood of the portal vein and its branches, but are not found in the general circulating blood of the finger or of the ear.

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(*b*) *Bacteria*

In general bacterial infections, there are bacteria in the circulating blood, but only occasionally are these recognizable, microscopically, in fresh or stained preparations (*Spirilla* of relapsing fever; *Treponema pallidum* of syphilis; *anthrax bacilli;* rarely, *tubercle bacilli*). The others (especially *typhoid bacilli* and the *pyogenic microörganisms* of septic infections) must be isolated by cultural methods.

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[NOTE.—See also references under Blood Cultures and under Tuberculosis in Part IV.]

(c) *Foreign Particles*

A black *pigment,* probably *hematin,* is sometimes seen free in the blood, sometimes encased in leukocytes, in malarial invasions.

During digestion, extremely minute *fat droplets* may be seen dancing about in the blood plasma in fresh preparations. The so-called *hemoconia,* or "blood-dust" of Müller, we have already described.

13. Bacteriological and Serological Examinations of the Blood

The five most important clinical methods coming under this category are: (a) *blood cultures,* to demonstrate the presence, or absence, of bacteria; (b) *agglutination tests,* especially, the Widal reaction in typhoid fever; (c) *precipitin reactions,* especially those used to distinguish human from animal blood, in medico-legal cases; (d) *complement-fixation tests,* for detecting the presence of specific antibodies (and also specific antigens), especially the Wassermann reaction for syphilis; and (e) *Abderhalden's reaction* for specific ferments, especially for (I) the ferments that will hydrolize placental protein (diagnosis of pregnancy); and (II) the ferment that will hydrolyze the protein from carcinomatous tissue (diagnosis of cancer). The first four of these methods, as well as other immunity-reactions, have been discussed in the section dealing with the diagnosis of infectious diseases; the fifth, Abderhalden's reaction, will be described here.

Abderhalden's Reaction

In 1912, Emil Abderhalden published his *dialysis procedure* for the demonstration of defensive ferments in the blood serum and other fluids of the body. This procedure, which he had gradually worked out during the preceding twelve years before publishing it, is based upon a simple theory.

Theory.—The blood maintains, with astonishing accuracy, its normal composition. When various substances (*e. g.*, water, sugar, etc.) suddenly

enter the blood, in large amounts, the normal composition is restored in an astonishingly short time by excretion, diffusion, etc.; but if substances entirely foreign to the blood, either substances foreign to the body as a whole, or pathological substances arising in the body itself, in either case, material foreign to the plasma (*e. g.*, pathological thyroid secretion, carcinoma protein, etc.) gain entrance to it, and are not easily gotten rid of, "defensive ferments" are formed, whose function it is to disintegrate substances foreign to the plasma, to rob them of their specific structure and to change them into a condition that will permit of their excretion. Obviously, these ferments must be strictly specifically adapted to the substances for which they are formed.

The demonstration of these ferments is now actually possible either through (1) Abderhalden's dialysis-procedure, or (2) Abderhalden's optic method.

i. Aberhalden's Dialysis Procedure

The method (Abderhalden reaction) is very simple in principle, but practically very subtle, delicate, and exposed to a great number of sources of error. (Fig. 305.)

In a small Erlenmeyer flask (*a*), especially made for the purpose, is placed 20 c.c. of sterile distilled water (*c*). In this is put a clean sterile dialysing tube or thimble (*b*), containing 1.5 c.c. of serum (*f*) from the patient to be examined. In the serum is placed a small piece of organ or tissue (*e*), corresponding to the origin of the foreign substance suspected to have gained entrance to the plasma and to have excited the production of a specific ferment to disintegrate it. For example, if one were attempting to make a differential diagnosis between carcinoma and simple ulcer of the stomach, one would test some of the patient's serum with a piece of carcinoma tissue in one thimble, and another portion of his serum with a piece of normal gastric mucous membrane, in a second thimble. These bits of tissue are prepared in such a way as to be absolutely free from blood and from peptone. The water (*c*) and the serum (*f*) in the thimble are now covered with a layer of toluol (*d* and *g*), and the whole apparatus is left for 16 hours, at exactly 37° C., in the thermostat.

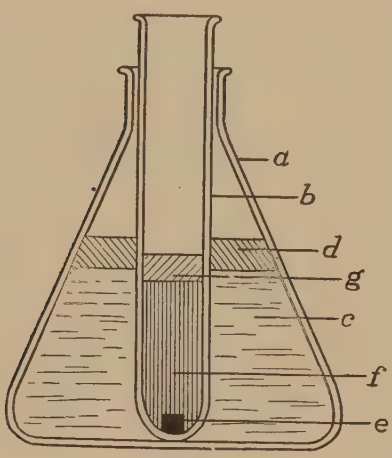

Fig. 305.—Diagram Illustrating the Method of Testing for Specific Defensive Ferments by the "Dialysis Proceeding." (Abderhalden's Reaction.)

If the serum contain a ferment capable of hydrolysing the tissue used, it will, at the end of 16 hours, have hydrolysed a part of this tissue, and the resulting peptone will have dialysed out into the water outside the thimble (*c*). The content of this water in peptone can be determined by the use of a very sensitive "ninhydrin reaction," which is capable of recognizing peptone in dilutions of 1:65,000. If the reaction be positive, and the two control tests, (1) serum without tissue, and (2) serum plus physiological salt solution, are negative, the existence of the suspected defensive ferment in the serum of the patient concerned is proven. Important diagnostic conclusions can obviously be made.

The test has thus far been chiefly applied in the early diagnosis of *pregnancy* (use of placental protein), and in the early diagnosis of *carcinoma* (use of carcinoma tissue), but a large number of investigators, notable among them Lampé of Munich, have been applying the reaction to the discovery of specific ferments in the serum for the *various tissues* of the body, especially those of the *endocrine glands* concerned in the formation of the internal secretions.

During 1913, Dr. Karl v. Noorden, Jr., applied the technic in my service at the Johns Hopkins Hospital, and some experiments have also been made in Baltimore by Dr. Judd and by Dr. S. R. Miller. I have been very much impressed with the large number of precautions that must be taken in order that errors may be avoided. The technic is so subtle, that no one should attempt it unless he can devote his undivided attention to it, at least for months. This is even more requisite than with the Wassermann reaction. Obviously, the general practitioner cannot himself be expected to perform such tests, but it may be that skilled workers in laboratories in the larger cities will make it possible for the practitioner to have blood examined for him for Abderhalden's reactions in special cases. It is too early as yet to pass final judgment upon the value of the method; but, certainly, no other new method has in recent times attracted so much attention as this among clinicians.

It would be out of place, in this text-book, to go into the enormous number of details that must be observed in testing for Abderhalden's reaction; at least twenty pages of this volume would be required. The full details are to be found in the last edition of Abderhalden's monograph on the subject, and, fortunately, this has been translated into English (See reference).

I cannot help but feel doubt as to the practical value of a method, the technic of which is so difficult.

ii. Abderhalden's Optic Method

A second method, known as the optic method, can be used as a control of Abderhalden's dialysis procedure. In principle, it consists of following

changes in optically-active substances, by determining alterations in the rotatory power by means of a polarization apparatus.

When defensive ferments act upon a colloid, they change it into a diffusable crystalloid, which, as we have seen, can be tested for, qualitatively, by the dialysis procedure.

In the optic method, the test cannot begin with protein, but must begin with a peptone prepared from the specific protein concerned.

The technic of the method is very simple. In a test tube is placed 1 c.c. of sterile blood serum, absolutely free from hemoglobin and from blood corpuscles. To this is added 1 c.c. of a 5-10 per cent peptone solution, made from the organ, or the protein, against which a defensive ferment is suspected to be present. The serum and the peptone solution are thoroughly mixed, and the mixture poured into a 2 c.c. polarization tube. The rotation of the mixture is measured as soon as the temperature has reached 37°C., and at regular intervals thereafter. If, after some time, no alteration in the rotatory power develop, we can assume that no fermentative hydrolysis has taken place. If, however, after a time, the rotatory power differs from that at the beginning of the test, we can conclude that a fermentative degradation has occurred. For the details of this method, the original publication should be consulted.

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C. Methods of Examining the Blood Clinically Important, but Less Frequently Employed

We shall consider here: (1) the determination of the coagulation time; (2) the determination of the viscosity of the blood; (3) the testing of the resistance of the red corpuscles to anisotonic solutions; and (4) the determination of the response of the red corpuscles to iso-agglutinins (and isohemolysins).

1. Determination of Coagulation Time

The methods devised for this purpose are not very reliable. Since the original method was introduced by Vierordt, various modifications have been employed. Of these may be mentioned those of Wright, Brodie and

Russell, Boggs, Bürker, Hinman and Sladen, Kottman, and Howell. The number indicates how unsatisfactory our state of knowledge here is.

(*a*) *Wright's Method*

A little blood is sucked into several capillary tubes of equal caliber. The blood is blown out of one tube after another, say every half minute or every minute, until, finally, a capillary tube is reached that is plugged by a blood clot.

Methods similar to Wright's are used by Sabrazès and by Schultz. Wright found the coagulation time, by this method, to vary, in normal cases, between 2½ and 6 minutes; in hemophilia, he found a coagulation time of 9-10 minutes. This method is not used clinically in this country.

(*b*) *Brodie and Russell's Method*

A hanging drop of blood, in a moist chamber, is exposed to a feeble tangential current of air sufficient to set the red corpuscles in rotary motion, and is observed under the microscope until the movement of the red corpuscles is interfered with by the fibrin formation. Modifications of this method have been suggested by Pratt, by Grützner, and by Boggs. The best instrument involving this principle is probably that of Boggs.

i. The Coagulometer of Boggs

This is a modification of Brodie and Russell's instrument. It consists of a moist chamber into which a truncated glass cone projects from above, terminating in a surface 4 mm. in diameter. A metal tube projects into the chamber from the side; it ends in a tip which comes close to the lower surface of the cone just mentioned. To the outer end of this metal tube is attached a rubber tube and bulb, through which a current of air may be directed, tangentially, toward the lower surface of the cone. A cover-glass is attached to the upper surface of the cone; at the edge of it there is a pinhole opening. To test the coagulation time a drop of blood is placed upon the lower surface of the glass cone, the cone is adjusted in the chamber, and the instrument placed on the stage of the microscope. One observes the

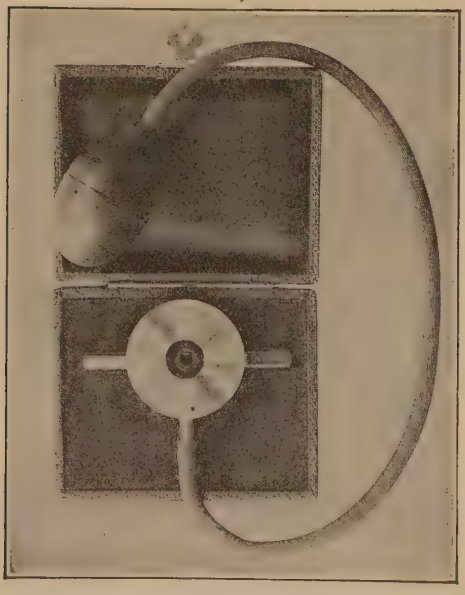

Fig. 306.—Bogg's Coagulometer with Bulb Attached, Viewed from Above.

drop under a low power, and by squeezing the bulb, directs a current of air against its edge; this starts the corpuscles into lively movement in a circular direction. As soon as fibrin begins to form, the movement of the single cells ceases, and the corpuscles begin to move in large masses, and, later still, these masses tend to become fixed, so that, though they are dislocated in the direction of the air current, they spring back as soon as pressure on the bulb ceases. This is close to the end-point, which is reached when a very gentle air current causes radial elastic motion like that "of a rubber ball pressed in at one point and released." Figures illustrating the movement of the corpuscles, of the masses and of the end-point are given in Emerson's "Clinical Diagnosis," and in Morris's "Clinical Laboratory Methods." The time elapsing from the moment the drop of blood appears in the wound to this end-point is known as the "coagulation time."

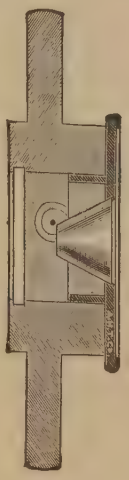

Fig. 307. Bogg's Modification of the Brodie - Russell Coagulometer. Photographed from the Side. (By courtesy of A. H. Thomas Co., Philadelphia.)

One now removes the cone, wipes off the drop of blood with a soft cloth, or with filter-paper, confirming at the same time the existence of a clot. Should the coagulation not be complete, the result should be discarded and another determination made.

With normal blood this instrument of Boggs shows a coagulation time varying between 3 and 8 minutes, averaging about 5 minutes.

In taking the drop of blood, the finger should be hyperemic, so that the blood will flow freely from the puncture. A little practice is needed in order to secure a drop of constant size when the blood is touched with the cone at right angles to its surface. No pressure is permissible in obtaining the drop of blood, as the admixture of lymph shortens the coagulation time. It goes without saying that the apparatus should be absolutely clean. In making pressure upon the bulb, only a gentle current of air should be produced, at not too frequent intervals—not oftener than every 30 seconds.

(*c*) *Bürker's Method*

In the concavity of a hollow ground glass, on a small rotating table, is placed a drop of distilled water, and, into this, a drop of blood from the finger-tip is allowed to fall. Every 30 seconds one passes a long-drawn-out, but blunt, glass rod through the mixture, the little table being rotated each time about 90 degrees. When coagulation sets in, a thread of fibrin is lifted up by the glass rod. With maintenance of a temperature of 25° C., the normal coagulation time by this method was found by Bürker to be 6-7 minutes. This method is not used clinically in this country.

(*d*) *Hinman and Sladen's Modification of Milian's Method*

The hyperemic ear-lobule is punctured, the first drop of blood that appears is wiped off, and the second drop is touched by the under surface of an ordinary clean glass slide in several places, a small droplet being collected at each place. The slide is then turned over quickly to prevent the drops from running. By superimposing the slide upon a millimeter scale, droplets having diameters of 4-5 mm. are selected; the other drops are wiped off. The slide is then held vertically.

One may observe the profile of the drop, which sags, looking like a falling tear, previous to coagulation, and, as soon as coagulation is complete, assumes a uniform convexity. Or, he may examine the droplet by transmitted light; before coagulation takes place, the dependent part of the drop looks denser; as soon as coagulation has occurred, the center of the drop will be the most dense part. Coagulation is confirmed by the transfer of the drop to a piece of linen, or of filter paper.

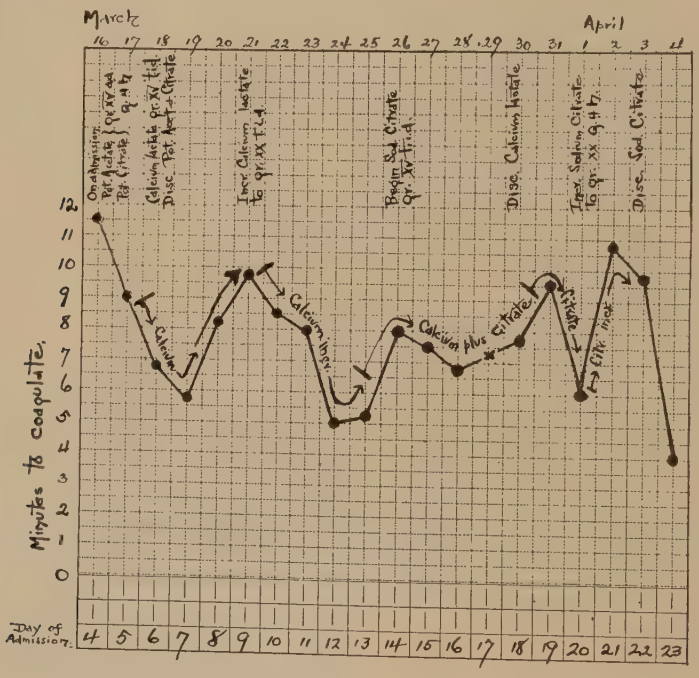

Fig. 308.—Effect of Drugs on Coagulation Time in a Case of Erythema nodosum. (After F. Hinman and F. J. Sladen, J. H. H. Bull.)

Hinman and Sladen examine several drops of 4 mm. and 5 mm. in diameter, the former coagulating more rapidly than the latter. The mean of the coagulation times required for the several drops is called the "coagulation time of the blood." Any coagulation time under eight minutes is regarded as normal; if more than eight minutes be required, coagulation is said to be pathologically delayed. In normal cases, the coagulation time found varies usually between five and eight minutes.

(e) *The Coagulo-Viscosimeter of Kottman*

By this instrument the beginning and the development of the coagulation of the blood can be quantitatively followed in their time relations. For the use of the instrument, the original article by Kottman should be consulted.

(f) *Howell's Method*

Probably the most accurate method of determining coagulation time is that recommended by Howell (Arch. Int. Med., xiii, 1914, p. 80). Two or four c.c. of blood are aspirated directly from the median basilic vein into a sterile syringe and then immediately expelled from the syringe into a wide tube (21 mm. diameter), which has been especially cleaned with a bichromate-acid mixture. The period elapsing between the moment the blood is drawn and the moment at which a clot has formed that is firm enough to permit the tube to be inverted, is regarded as the "coagulation time" (Howell). By this method, the coagulation time (Howell) of normal blood, varies between 20 and 40 minutes. "Reliable results are obtained only in those cases in which the needle of the syringe enters the vein readily on the first puncture."

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2. Viscosimetry, or the Determination of the Viscosity of the Blood (η), and of the Serum (η_1)

The determination of the viscosity, or internal friction, of the blood and of the blood serum is of considerable value (see introductory note on Physical Properties of the Blood). The original method for measuring viscosity involved the use of Ostwald's apparatus. For work on experimental animals, a special apparatus has been devised by Burton-Opitz of Columbia University, New Yorrk.

Most of the recent clinical observations have, however, been made by (1) the viscosimeter of Hirsch and Beck; (2) that of Determann; (3) that of Hess, and (4) that of Determann and Hess. Only the two latter methods will be described.

(*a*) *Method of W. Hess*

With Hess's instrument, the relative viscosity of the blood to that of water is determined, and the result read off directly. The apparatus is well shown in Fig. 309.

By means of the rubber bulb (Gb), water is sucked in from a pipet into the glass tube (G) (the stop-cock (H) being open), as far as the capillary tube (K_1); then, water is sucked through the capillary tube as far as the mark O on the calibrated tube (M_1). The suction is now interrupted, and the stop-cock (H)

closed, the tube (E), which can be removed from the instrument and is interchangeable with other tubes of the same sort, being held in position by the spring (F).

The hyperemic finger-tip is pricked just deeply enough to permit a droplet of blood to flow freely out. This is taken up by the smooth end of the tube (E), the blood being allowed to flow in spontaneously until the tube is ¾ full of blood. The tube is next turned upside down, so that the blood flows to the other end, and begins to come out, when it is at once attached to the capillary tube (K_2), and fixed in place by means of the spring (F). By suction, the blood is drawn through the capillary tube (K_2) as far as the mark 0 on the tube (M_2); the suction is then interrupted.

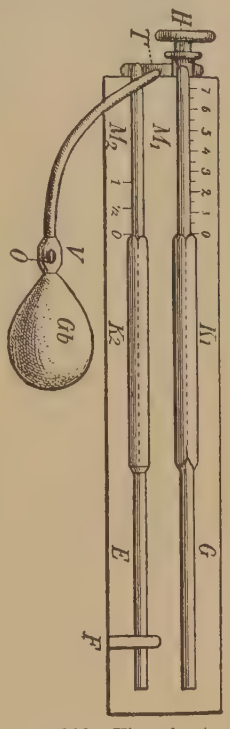

Fig. 309.—Viscosimeter of Hess. (After P. Krause, "Klinische Diagnostik." Published by G. Fischer, Jena.)

The stop-cock (H) is now opened, after which the contents of both tubes (water in one, blood in the other) can be exposed to exactly the same suction- or pressure-influences. Suction is started, and is continued until the blood reaches the mark 1; it is then interrupted, and one reads off on the scale the distance to which the water has, during the same suction, travelled. The result is the degree of viscosity of the blood under examination.

The stop-cock (H) is now closed, the blood is pressed out into a piece of linen, the little tube (E) is taken off, and ammonia is sucked twice through the capillary (K_2) and the calibrated tube (M_2) and pressed out again; a little more ammonia is then sucked in, and the free end of the tube is closed by a rubber cap. To make another determination, the water is again adjusted to the zero point, the stop-cock is closed, the ammonia removed, and another blood tube put in.

The greatest cleanliness is essential, if reliable results are to be obtained. Every now and then the apparatus should be thoroughly cleaned with strong nitric acid. If only a little blood be obtainable, or, if the blood be very concentrated, it may be sucked in as far as the mark ½; the number on the water scale at the end of the suction is then multiplied by 2.

It is desirable that the work be done at a constant temperature; determinations made at the room temperature of about 17° C. (62.6° F.) are subject to an error of about 4 per cent.

(*b*) *The New Determann-Hess Viscosimeter*

In this instrument, the principles of the old Determann apparatus, and of the Hess apparatus, are combined. Gravity is used as the driving force. It acts simultaneously upon two fluid columns (I and II, at A, Fig. 310), which flow through two adjacent capillaries, *a* and *b*, of the same length, and of the same caliber. These capillaries open into small tubes, marked by a centimeter scale. After filling the water-mantle *c* with water at 20° C., blood is sucked in to the non-calibrated end of the tube I, and distilled water into tube II. In each case, the fluid is sucked in as far as the beginning of the capillary.

The amount of blood required is about 0.1 c.c. This blood is best obtained from the finger-tip, made hyperemic by a warm hand-bath. All stasis, and all pressure, should be avoided. If desired, the blood may be made non-coagulable by gently rubbing into the blood droplet a granule of hirudin placed on the end of the tube, though on working quickly, this is not necessary; or, if the blood be drawn from a vein at the bend of the elbow, one can place a little hirudin upon the piston of the syringe. Inclining the apparatus away from the horizontal, one can, by alternately shutting and opening the capillary tubes, bring the ends of both columns of fluid to the zero-point of the scale; this is very easy after a little practice.

Fig. 310 Viscosimeter of Determann. (After P. Krause, "Klinische Diagnostik." Publisned by G. Fischer, Jena.)

The apparatus is now suddenly set upright, and the blood is allowed to flow as far as the mark 1 on the centimeter scale. The tubes are then made horizontal again, and one looks to see to what mark on the scale the distilled water has attained. On reading off the number we at once have the degree of the relative viscosity of the blood under examination.

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3. Determination of the Resistance of the Red Blood-Corpuscles in Anisotonic Solutions

The principle involved has already been discussed under the Physical Properties of the Blood (*q. v.*).

The importance of these resistance determinations has been especially emphasized by the French school, particularly in connection with congenital hemolytic jaundice. Moss's modification of von Limbeck's method is the procedure I advise.

(*a*) *Hamburger's Method*

Into each of a series of conical glass vessels (each containing 2 c.c. of salt solution, the concentration showing an increase of 0.01 per cent NaCl in each vessel of the series), a small quantity (0.05 c.c.) of blood is introduced by means of a calibrated pipet; after standing for fifteen minutes, the tubes are all centrifugalized. The tube containing the solution that is just colorless, that is, showing no hemolysis, indicates the resistance limit.

(*b*) *von Limbeck's Method*

Here 1 c.c. of salt solution is placed in each of a series of test tubes, the strength of the solution changing for each tube; one drop of defibrinated blood is then added to each tube. The concentrations of the salt solution extend from 0.2 per cent to 0.85-per-cent NaCl; the difference between the concentration of one tube, and that of the next, amounts always to 0.03 per cent. The tubes are allowed to stand for six hours; then the hemolytic limit is noted.

An easy method for making salt solutions of different concentration is that used by W. L. Moss (1911):

Tube No.	Solution of 1% NaCl.	Distilled Water	Resultant Dilution
1	7.5 c.c.	2.5 c.c.	0.75%
2	7. "	3. "	0.7 %
3	6.5 "	3.5 "	0.65%
4	6. "	4. "	0.6 %
5	5.5 "	4.5 "	0.55%
6	5. "	5. "	0.5 %
7	4.5 "	5.5 "	0.45%
8	4. "	6. "	0.4 %
9	3.5 "	6.5 "	0.35%
10	3. "	7. "	0.3 %
11	2.5 "	7.5 "	0.25%
12	2. "	8. "	0.2 %

Normally, the minimal resistance is about 0.47 per cent NaCl; the maximal, 0.3 per cent NaCl.

(*c*) *Janowski's Method*

A blood count is first made in the ordinary way; afterwards, blood counts are made by diluting the blood 1:200 in salt solution of three strengths, 0.4 per cent, 0.35 per cent, and 0.3 per cent. The number of red blood-corpuscles dissolved, in each instance, is thus determined.

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4. Determination of the Response of the Red Blood Corpuscles to Iso-agglutinins and Isohemolysins

When making blood transfusions, it is important, if possible, to select a donor who belongs to the same iso-agglutinin group as the recipient (W. L. Moss). A full account of the exact method of determining these groups is to be found in Moss's papers in the Johns Hopkins Hospital Bulletin.

If for any reason the exact group cannot be determined, the safety of the blood of the donor for the recipient may be tested for as follows:—

(1) Collect a few drops of the patient's blood in a glass tube, in the same way as for a Widal reaction; after coagulation has occurred and the clot separated, the serum is ready for testing.

(2) Collect one or two drops of the patient's blood in a centrifuge tube containing a few cubic centimeters of 1.5 per cent sodium citrate dissolved in a 0.85-per-cent solution NaCl. Wash the corpuscles thus obtained twice in normal salt solution by centrifugalizing, and then make an approximately 1-per-cent suspension of corpuscles in normal salt solution.

(3) Collect in a similar way serum and corpuscles from the prospective donors.

(4) Test the agglutinating action of the serum of the patient against the corpuscles of each of the prospective donors.

(5) Test the serum of each of the donors for its agglutinating action against the corpuscles of the patient.

In making these agglutination tests one uses the hanging-drop method, a small drop of the serum being added to an equal quantity of the suspension of corpuscles; the presence or absence of agglutination is observed under the microscope at the end of one hour.

In interpreting the results, if the serum of individual A does not agglutinate the corpuscles of individual B, and if B's serum does not agglutinate A's corpuscles, the two individuals belong to the same iso-agglutinin group. As Moss points out, it is not necessary to test for isohemolysins, since it

has been shown that, if isohemolysin be present, it follows the same laws as those that govern iso-agglutin.

Recently, a simple and expeditious method has been suggested by Dr. Peyton Rous and J. R. Turner (see reference).

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D. Methods of Examining the Blood Only Occasionally, as yet, Resorted to Clinically

A number of methods occasionally resorted to, especially in research work, may now be very briefly referred to, and references will be given to original articles, which may be consulted by those who desire to employ them. It seems wiser to deal with these methods in this way rather than to burden this volume with full descriptions of them.

1. Determination of the Total Amount of Blood in the Human Body

Any one of several methods may be employed for clinical determinations:

(a) The method of Morawitz, who calculates it from the volume per cent of the arm-blood, as determined with the plethysmograph.

(b) The method of Haldane and Smith, with carbon monoxid.

(c) The method by inhalation of CO of Zuntz and Plesch.

(d) The colorimetric method of Plesch (1909), in which the blood is diluted and the relative diminution of the color in comparison with that of the undiluted blood is established with the chromophotometer.

(e) The application of the optical method of Abderhalden and Schmid (1910), in which a 25-per-cent solution of dextrin in physiological salt solution is injected into the blood; the specific rotation of the plasma before and after injection permits of a calculation of the total amount of blood.

(f) The antitoxin method of von Behring, in which the total amount of blood is calculated from its antitoxin content after intravenous injection of a known amount of tetanus antitoxin.

(g) Recently (1915) N. M. Keith, L. G. Rowntree and J. T. Geraghty have devised an ingenious and simple method for the determination of plasma and blood volume, which yields very accurate results and seems destined to supplant the older and less clinically applicable methods. The principle underlying this method is the introduction directly into the circulation of a non-toxic, slowly absorbable dye (vital red), which remains in the plasma long enough for thorough mixing, and the determination of its concentration in the plasma colorimetrically by comparison of a suitable standard mixture of dye and serum.

Probably the most convenient and least harmful methods are (d) Plesch's colorimetric method, (e) Abderhalden and Schmid's method, and (g) the method of Keith, Rowntree and Geraghty.

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2. Volume of the Blood Corpuscles and of the Plasma

(*a*) *Hematocrit Method* (*Blix-Hedin, Daland, Capps*)

The blood is collected in a graduated capillary tube and centrifugalized. The internal diameter of the capillary tube is 1 mm.; in the calibration it is divided into 50 equal parts. After centrifugalization, one reads off the volume of the formed elements in the centrifugate. In Deland's hematocrit, the tube is divided into 100 equal portions, each division of the scale representing roughly 100,000 normal red corpuscles. To avoid coagulation, a granule of hirudin is mixed with the blood droplet; or, the blood may be mixed with an equal volume of 2.5-per-cent solution of potassium bichromate, or, if preferred, with an 0.92-per-cent isotonic salt solution; with these dilutions the readings must be correspondingly corrected.

To obtain comparable results, a centrifugal apparatus with ten thousand revolutions per minute is required; and the centrifugalization must be always carried on for the same length of time, and at the same speed. The volume-quotient (Capps) has already been described. For the details of the method, Capp's article should be consulted.

Emerson uses the hematocrit for separating the corpuscles from the plasma when lipemia, cholemia, or hemaglobinemia is suspected.

(*b*) *Method of Sedimentation in the Blood-voluminimeter* (*Biernacki; Grawitz*)

(1) Collect a few c. c. of blood.

(2) Add a little dry sodium oxalate (0.2 per cent), to prevent coagulation.

(3) Allow to stand for 24 to 48 hours in a graduated glass cylinder known as a blood-voluminimeter (Grawitz). The volume of corpuscles and of plasma are then read off.

(*c*) *The Electrical Conductivity Method*

Since the R. B. C. diminish the electrical conductivity of the blood serum in a constant way, according to their volume, the determination of the electrical conductivity can be used also for determining the volume of the R. B. C. (Bugarszky and Tangl).

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3. The Determination of the Total Solids (Dried Residue) and of the Water-Content of the Whole Blood of the Plasma and of the Serum

A small quantity (½ c. c.) of whole blood, plasma or serum, is exactly weighed, and dried for several days to constant weight in an exsiccator over H_2SO_4 or $CaCO_2$, and the residue subsequently weighed.

The best method is probably that of L. F. Shackell (1909), which excludes the possibility of injuring the constituents of the blood. He freezes the blood in a mixture of ice and salt, then places it in an H_2SO_4-exsiccator, and exhausts the air with a mercury pump, until the pressure is reduced to a small fraction of a millimeter. In 4 days, the desiccation will have gone on to constant weight.

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4. The Determination of the Specific Gravity of the Blood and of the Serum

(*a*) *Method of Hammerschlag*

Clinically, Hammerschlag's method is commonly employed.

(1) Prepare a mixture of chloroform (sp. gr. 1,526) and benzol (sp. gr. 0,88) so that it has a sp. gr. of 1,056.

(2) Allow a drop of blood to fall into this mixture; if it sinks, the specific gravity is greater than 1,056; if it floats it is less.

(3) Add chloroform or benzol as required until a mixture having the same specific gravity as the blood is reached, that is, until the drop of blood "neither floats nor sinks." (For the precautions to be used see the article by Zuntz.)

(*b*) *Method of Schmaltz*

More accurate results can be obtained by the use of the capillary pyknometer of Schmaltz, a small tube with open, flattened ends, containing about 0.2 g.

(1) Clean the tube with alcohol and ether, dry and weigh.

(2) Fill the tube with distilled water (15° C.) and weigh.

(3) Dry the tube again; fill it with blood; wipe ends of tubes; weigh.

The absolute weight of the blood, divided by the weight of the water, gives the specific gravity of the blood.

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5. Determination of the Actual, and of the Potential Alkalinity of the Blood

From the standpoint of pure physical chemistry the blood is neutral, but, on titration with ordinary indicators, it yields an alkaline reaction. (For explanation see Physical Properties of the Blood).

(*a*) *The Actual Reaction of the Blood* (*Quantitative Determination of H- and of OH-Ions*)

For exact determination, it is necessary to use the "gas-chain" method of measurement, as applied by L. Michaelis; instead of his gas electrode, the electrode of Hasselbach (1910) may be used. As far as I know, the indicator method of Sörensen has not been much applied to blood; there would be two main difficulties (absorption of the indicator by colloids and masking of the indicator color by the color of the blood).

i. Levy, Rowntree and Marriott's Simple Method for Determining Variations in the Hydrogen-ion Concentration of the Blood

Principle of the Method.—By means of dialysis against 0.8-per-cent salt solution the proteins and coloring matter of the blood are excluded from the dialysate, which contains salts and is well adapted to the use of an indicator. Phenolsulphonephthalein is added to the dialysate, and the solution so obtained is compared with a series of standard colors of known hydrogen-ion concentration until the corresponding color is found.

Materials Required.—1. Standard Colors.—These are prepared as follows:

(a) 1/15 mol. acid (or primary) potassium phosphate. 9.078 grams of the pure recrystallized salt (KH_2PO_4) are dissolved in freshly-distilled water and made up to 1 liter.

(b) 1/15 mol. alkaline (or secondary) sodium phosphate. The pure recrystallized salt ($Na_2HPO_4 \cdot 12\ H_2O$) is exposed to the air, protected from dust, for from ten days to two weeks. 11.876 grams are then dissolved in freshly-distilled water and made up to 1 liter.

If sufficiently pure, the solutions will give a deep rose-red color with phenolphthalein.

The solutions are mixed in the proportions indicated below, to obtain the desired pH:[1]

pH	6.4	6.6	6.8	7.0	7.1	7.2	7.3	7.4	7.5	7.6	7.7	7.8	8.0	8.2	8.4
Primary Potass. Phos., c.c.	73	63	51	37	32	27	23	19	15.8	13.2	11.0	8.8	5.6	3.2	2.0
Secondary Sod. Phos., c.c.	27	37	49	63	68	73	77	81	84.2	86.8	89.0	91.2	94.4	96.8	98.0

Three c.c. of each of the mixed solutions thus obtained are placed in suitable test tubes (100 × 10 m.m., inside measurement). Five drops of an aqueous 0.01-per-cent solution of phenolsulphonephthalein are added to each tube. The tops are sealed off. The series of colors representing different concentrations of hydrogen-ions constitute the standards for comparison.

2. Collodion Sacs.—One ounce of celloidin (Anthony's negative cotton) is dissolved in 500 c.c. of a mixture of equal quantities of ether and ethyl alcohol. The solution should stand for at least three or four days, after which the clear supernatant solution is ready for use. A small test tube (120 × 9 mm., inside measurement) is filled with this mixture, inverted, and half the contents are poured out. The tube is then righted and the collodion allowed to fill the lower half again. A second time it is inverted and rotated on its vertical axis, the collodion being drained off. The tube is then clamped in the inverted position and allowed to stand for ten minutes. It is filled five or six times with cold water, a knife-blade is run around the upper rim, and a few c.c. of water are run down between the sac

[1] To avoid writing large figures it is customary to use the logarithmic notation and to express, for example, $\frac{1}{10{,}000{,}000}$ N as 10^{-7}N, or, more conveniently, as suggested by Sörenson, to drop the 10 and minus sign and say pH7. The higher the exponent, the more alkaline, or, what is saying the same thing, the less acid is the solution.

and the glass of the tube. By gentle pulling the tube is extracted, after which it is preserved by complete immersion in water.

3. Salt Solution.—An 0.8-per-cent solution of sodium chlorid is employed. This must be free from alkali and from acids other than carbonic. It is best kept in a Jena glass flask, protected from acids in the air by means of a soda lime tube.

Technic of the Method.—The determination may be carried out on serum, or on whole blood, (oxalated).* The work must be done in a room free from fumes of acids or ammonia. One to three c.c. of clear serum or of blood is run, by means of a blunt-pointed pipet, into a dialyzing sac, which has been washed inside and outside with salt solution, and which has been tested for leaks by filling with salt solution. The sac is lowered into a small test tube (100 × 10 mm., inside measurement), containing 3 c.c. of the salt solution, until the fluid on the outside of the sac is as high as the fluid on the inside. It is allowed to remain five minutes. The sac is removed and five drops of the indicator are thoroughly mixed with the dialysate. The tube is then compared with the series of standards until the corresponding color is found. This indicates the hydrogen-ion concentration present in the dialysate, and for practical purposes may be regarded as the hydrogen-ion concentration of the blood or serum on which the determination has been carried out.

Results Obtained with the Method.—Oxalated blood from normal persons gives a dialysate with a hydrogen-ion concentration varying from 7.4 to 7.6, while that of serum ranges from 7.6 to 7.8. In a small series of cases of clinical acidosis in which the test has been carried out, the serums have varied from 7.55 to 7.05 and the oxalated bloods from 7.3 to 7.05.

(*b*) *The Potential Reaction of the Blood*

Aside from the exact methods of physical chemistry, several methods have been used for determining the alkalinity, or acid-capacity, of the blood. Some of these deal with unaltered blood, others with laked blood. These methods measure the sum of the actual ions (see above) and of the potential ions.

Probably the best clue to "acidosis" can be gained by applying Van Slyke's method of determining the carbonate content of the serum.

i. Loewy's Method

(1) Collect 5 c.c. blood in a 50 c.c. flask with graduated neck containing 45 c.c. ammonium-oxalate solution (0.25 per cent) to prevent coagulation. Mix well.

(2) Take 5 c.c. of the mixture and titrate with N tartaric acid against lacmoid paper as an indicator. The end-reaction is indicated on the lacmoid paper by a sharp red line in the periphery of a drop of the fluid placed upon it.

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*The blood is collected in tubes containing a little dry powdered sodium oxalate (free from carbonate).

ii. Salkowsky's Method

By this method a definite amount of ammonium sulphate is added to the blood; ammonia is set free by the alkali of the blood and determined by Schlössing's method.

iii. Dare's Method

This is based upon the principle that the light-extinction of oxyhemoglobin on spectroscopic examination disappears at the point of exact neutralization of the blood. Dare's hemoalkalimeter is a simple instrument and deserves more attention than it has received. The details of its application are to be found in Dare's original article, and also in Ralph Webster's Diagnostic Methods.

iv. Sellard's Method

(1) To 1 c. c. of blood serum, add 24 parts of absolute ethyl alcohol. Mix well.
(2) Filter into a clean porcelain evaporating dish.
(3) To the filtrate add three drops of a 1-per-cent phenolphthalein solution and evaporate slowly to dryness over a steam-bath.

The results are valued as follows: (1) normal alkalinity—a pink color appears before evaporation to dryness; (2) slight reduction of alkalinity—a pink color appears just at dryness, but quickly disappears; it will reappear on the addition of a drop of water; (3) moderate reduction of alkalinity—no pink color appears even on drying, though if when dry a drop of water be added a pink color is assumed; (4) marked reduction of alkalinity—no pink color appears on drying or on adding a drop of water after drying.

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6. The Determination of the Volume and of the Tension of the Gases of the Blood

(*a*) *The Volume Per Cent of O_2 and CO_2*

The methods for determining these have been described under hemoglobin estimations.

(*b*) *The Tension of the Gases in the Blood*

For methods of measurement, see Loewy's article. See, also, reference above to Van Slyke.

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7. Determination of the Osmotic Pressure (Molecular Concentration) and of the Electrical Conductivity (Electrolytic Dissociation) of the Blood

The determination of the osmotic pressure (molecular content) may be made with Beckmann's apparatus or cryoscopy, by which the lowering of the freezing point is measured.

Electrical conductivity (ionic content) is determined by the Kohlrausch method, which makes use of a Wheatstone bridge with telephone, as in researches in physical chemistry. (For full particulars, consult Hamburger's "Osmotischer Druck und Ionenlehre"; also H. P. Jones's Physical Chemistry.)

8. Determination of the Content of Nitrogenous Substances in the Blood

One determines first the total nitrogen of the whole blood, of the plasma, and of the serum, and subsequently the so-called rest-nitrogen, or incoagulable nitrogen after removal of the coagulable protein substances. Separate determinations of globulins, albumins, ammonia, urea, amino-nitrogen, hippuric acid, total purins, uric acid, bile pigments and indican are made.

For clinical studies, one can work with small quantities of blood (about 5 c.c. of blood or blood serum) by Abderhalden's method. A full description of the methods will be found in F. Samuely's article in the second volume of Handb. d. biochem. Arbeitsmethoden (Abderhalden), 1910, 357-377.

(*a*) *Total Protein of the Blood*

i. Kjeldahl Method

Five c.c. of blood are exactly weighed and washed into a flask with distilled water. The total nitrogen is determined by Kjeldahl's method.

In another specimen of blood the amount of incoagulable nitrogen is determined (see below) and subtracted from the total nitrogen. The difference represents the nitrogen of the total protein.

ii. Microkjeldahl Method for Small Amounts of Blood or Other Nitrogen-containing Fluids

In recent years the development of micro-chemical methods has gone ahead with astonishing rapidity, thanks especially to the researches of Folin in Boston and of I. Bang and of Pregl in Europe. One of the most convenient of these micro-chemical methods is the one permitting of the use of a very small amount of protein-containing fluid for analysis. At my request, Dr. R. R. Snowden has written out an account of the microkjeldahl method used in the chemical division of the laboratory of the clinic in which I work. It is as follows:

Preliminary Digestion.—The substance containing the nitrogen is accurately measured into a 50 c. c. long neck, pear-shaped Kjeldahl flask, an amount being taken that will contain from two to fifteen milligrams of nitrogen. To this is added 2 c.c. of concentrated sulphuric acid (C.P.), about 1 gram of potassium sulphate (C.P.), and a small crystal of copper sulphate. The tip of the flame of

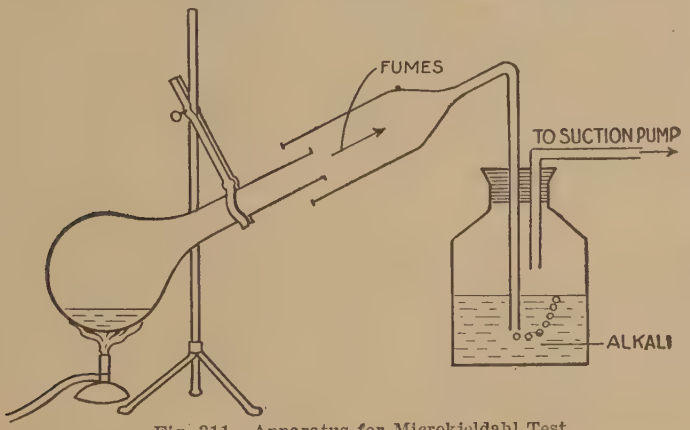

Fig. 311.—Apparatus for Microkjeldahl Test.

a micro-burner is then applied to the flask and the heating continued for two or three minutes after the mixture has become a clear blue. The arrangements for digestion and carrying off the fumes are illustrated in Figure 311. As will be seen, the flask is held in a clamp, placed midway on the neck, this clamp being fastened to an iron stand; by reason of the double joint in the clamp the flask can be tipped to any angle. During the digestion it is slanted in such a way that the neck of the flask opens within the fume absorber. The fumes are carried back by the air current and the acids are caught by the alkali, which thus protects the metallic parts of the pump.

When the digestion is complete, the mixture is allowed to cool, the flask is tipped to the upright position and 20 c. c. of distilled water are added. The ammonia is then collected in a standardized acid solution by means of combined distillation and aeration, the system being composed of glass tubing (diameter 3 mm.) and rubber corks, and so arranged that the air current first bubbles through the mixture in the Kjeldahl flask and then through the standard solution of acid. Fig. 311a shows the disconnected apparatus, rubber stopper "A" being of a size to fit snugly into the neck of the Kjeldahl flask, and thistle tube "B" being of such a length that the tip (drawn out fine) comes to within about 1 cm. of the bottom of the Kjeldahl flask. The second length of glass tubing, "C," begins 1 cm. below the stopper and, after emerging from the stopper, bends sharply downward and passes, after a second bend, through stopper "D," which

fits accurately into a Jena glass test tube (thin walled, 20 x 200 mm.). The glass tubing "C" reached to a point about 1 cm. from the bottom of the test tube, being drawn to a fairly fine tip, or ending in a small bulb through which are several small openings. The length of the glass tube, "C," should be as short as possible in order to reduce the error incident to the absorption of alkali from the glass during the distillation.

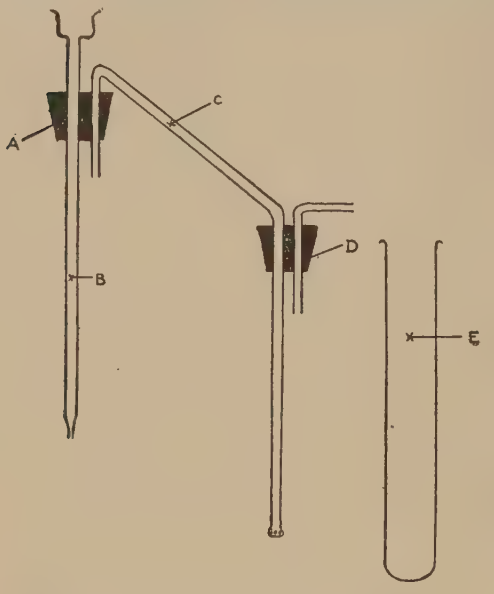

Fig. 311a.—Apparatus for Microkjeldahl Test.

Into the Jena glass test tube is accurately measured 20 c. c. of $\frac{N}{50}$ HCl, or $\frac{N}{10}$ HCl, depending on the amount of nitrogen that will be recovered. Into this tube is then fitted stopper "D" and the system is then arranged as in Fig. 311b, the test tube being almost submerged in ice water. A brisk air current is then started and into the thistle tube is poured 8 c. c. of 40-per-cent NaOH, neutralizing the excess of acid and liberating the ammonia. The flame is then applied to the Kjeldahl flask until vigorous boiling results, the steam being carried over with the air current and condensing in the acid solution. The ammonia, of course, is carried over with the steam and is caught by the acid. Even though some of the steam should pass through the acid without condensation, the ammonia will all be caught. If the boiling is too brisk and the steam comes over too rapidly, this will become evident by the fact that but few bubbles will reach the surface of the acid solution, the steam condensing at once. At this point the heat should be reduced, lest a positive pressure developed in the Kjeldahl flask and steam and ammonia escape back through the thistle tube. The air current reduces the tendency to foam, so that talcum power or glass beads are unnecessary.

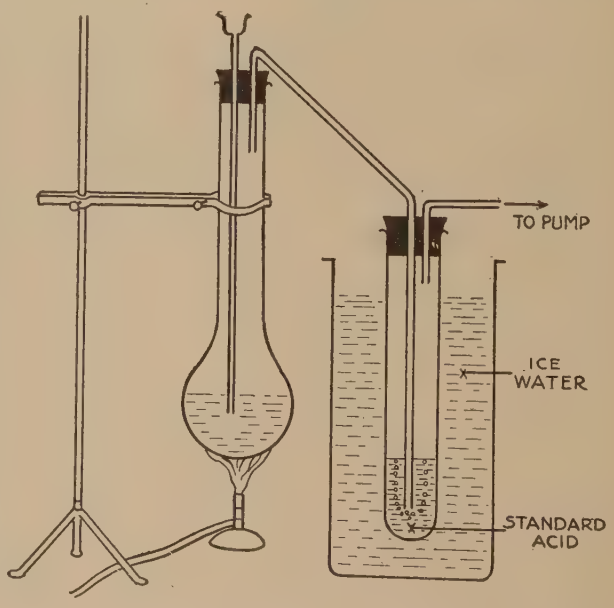

Fig. 311b.—Apparatus for Microkjeldahl Test.

The boiling is carried on until 10-15 c. c. have been distilled over. This can be roughly noted by the rise in the level of the fluid in the test tube. When thus complete, the air current is slowed and the stopper "A" disconnected. The test tube is then disconnected and the tip of the glass tube "C" is allowed to drain for 30 seconds against the side of the tube. The contents of the tube are then washed into a beaker and the excess of acid titrated with sodium hydrate, using cochineal as an indicator.

Discussion.—When the amount of nitrogen to be recovered lies between one and five milligrams, $\frac{N}{50}$ HCl is used to catch the ammonia, 20 c. c. being taken. If it lies between five and twenty milligrams, $\frac{N}{10}$ HCl is used, taking 20 c. c. When quantities less than a milligram are being determined, Nesslerization according to Folin's method is more accurate. The best results with titration are obtained when 5-10 mg. of nitrogen are present in the specimen.

This method requires as much time and more watching than the large Kjeldahl, the advantages being that smaller quantities of nitrogen can be taken and no elaborate or expensive apparatus is necessary. It can be easily carried out in a small laboratory or a physician's office, provided a good suction pump is at hand. The whole procedure can be completed within half an hour.

The method has been in use in the chemical laboratory of the hospital for some time and has been carefully checked up. Its error lies between one and two per cent, which is well within the limits of error present in the collection of clinical specimens.

iii. Refractometer Method (E. Reiss)

The protein content of the plasma or of the serum can be very satisfactorily determined by means of Pulfrich's refractometer. It must be understood that the refractometric examination is not a specific examination for protein, but is an estimation of the concentration of all the substances present in a fluid as expressed by the refraction of light. To calculate approximately the protein-content from this physical value is practicable only for fluids whose protein-content represents the main mass of all the dissolved substances, and in which the other dissolved substances are relatively constant in quantity and quality (E. Reiss). These conditions are fulfilled by blood serum, and less satisfactorily by exudates and transudates. The cerebrospinal fluid contains too little protein, and albuminous urine is too variable in its content of albumin, to permit of satisfactory refractometric estimations.

Protein has a relatively high refraction index. It is about as great as that of NaCl and larger than that of the other substances occurring in any quantity in blood serum. Refractometry requires only a very small amount of serum and is a very simple procedure, which can be rapidly carried out.

The sample of blood is taken from the patient fasting, in the morning (finger-tip or ear; no pressure), in a little tube like that used for collecting blood for a Widal test. It is well to fill two such tubes, 0.5 c.c. in each, so that one can be used for a control. The serum is separated from the blood by centrifugalization, or by longer standing. One or two drops of serum are dropped upon the refractometer prism, held perpendicularly. Then the accessory prism is set in place, the "beaker-mantle" applied, its cover closed, and the whole apparatus is placed in the water-bath. When the drop betwen the prisms has reached the temperature of the water-bath (17.5° C.), the reading is made. From Reiss's table, the percentage of protein can be directly calculated from the scale of the refractometer.

iv. Robertson's Refractrometric Method for Determination of Total Proteins, Total Albumins, Total Globulins and Total Non-proteins

Blood is collected in centrifuge tubes, permitted to clot, and centrifugalized. To a portion of clear serum, an equal volume of saturated solution of ammonium sulphate is added. This precipitates the globulins, the precipitate being removed by centrifugalization. A little of the supernatant fluid is diluted to one-half, and read in the refractometer. On correcting the reading for ammonium sulphate, the result gives the total albumin plus the non-proteins. The volume of the non-protein is determined from the clear fluid remaining after removal of the proteins from another portion of the serum by means of heat and acetic acid. The total globulins are obtained by subtracting the reading of the albumins on the refractometer from that of the whole serum after deducting the value of the non-proteins.

Tranter and Rowe, working with Robertson, find that in normal persons the total proteins range between 6.7 and 8.7 per cent; the total albumins lie between 4.95 and 7.7 per cent; the globulins lie between 1 and 2.54 per cent; and the non-proteins lie between 0.98 and 1.19 per cent, the refractivity averaging 0.00175.

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(*b*) *The Globulins and Albumins of the Blood*

For special purposes, it may be desirable to inform ourselves regarding (i) the fibrinogen, (ii) the thrombin, (iii) the antithrombin, (iv) the serum globulin, and (v) the serum albumin.

i. Fibrinogen Content of the Blood

For the best methods of determining fibrinogen in the blood, see the article by G. H. Whipple (Amer. Jour. Physiol., 1914, xxxiii, 50), and that by E. W. Goodpasture (Amer. Jour. Physiol., 1914, xxxiii, 70).

Quantitative methods of determining fibrinogen have been devised by Frederitig (fractional heat coagulation); by Doyan, Morel and Peju (precipitation by acetic acid; by Reye (1898) and by Porges and Spiro (salting out of plasma, treated with fluorid of sodium, with neutral ammonium sulphate solution); by Wohlgemuth (serial coagulation tubes of salt plasma obtained by mixing blood with 20-per-cent magnesium sulphate solution).

ii. Thrombin and Prothrombin Content of Blood

The best methods are those of W. H. Howell (Amer. Jour. Physiol., 1910, xxvi, 453; Arch. Int. Med., 1914, xiii, 76). For studies on prothrombin (or thrombogen), see Howell's articles, and also those of Morawitz, L. Loeb, Noef, Schmidt, and Wohlgemuth (1910).

iii. Antithrombin Content of Blood

See articles by W. H. Howell, (1910; 1914) and by G. H. Whipple (Arch. Int. Med., 1913, xii, 637).

iv. Serum Globulin

This can be determined by the method of Panzer, who devised it especially for the study of globulin in the cerebrospinal fluid (See Wien. klin. Wchnschr., 1899, 805-807.)

v. Serum Albumin

The total protein of the serum, less the serum globulin, gives the content in serum albumin. The method of separating different colloids by ultrafiltration (H. Bechold) might well be applied in hematology.

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(c) *Removal of Proteins from the Blood*

i. Removal of Proteins by Electro-positive Colloid Iron Hydroxid (Rona and Michaelis)

The method is applicable for serum, or for the whole blood, and is probably the best method available. It can be used, also, for milk, urine, and other protein-containing fluids.

(1) Collect 50 c. c. of blood serum, blood plasma, or whole blood and dilute with 12 or 14 volumes distilled water; record precisely the total volume of the fluid.

(2) Without changing the reaction, and without adding any salt of any sort, add 40 c. c., drop by drop, of liquor ferri oxyd. dial. (proven to be free from chlorin and from acid), shaking well during the addition. This completely precipitates the protein.

(3) Filter through a folded paper filter. The filtrate should be as clear as water, and should be free from both protein and iron. Its volume should be exactly determined and recorded.

Make the filtrate feebly acid with acetic acid and concentrate *in vacuo*, or on the water-bath, to 4-6 c. c. This can be done without darkening the color of the fluid, and the concentrate can be used for polarization experiments if desired. (For details, see Rona (P.) and Michaelis (L.), Biochem. Ztschr., 1908, vii, 329; xiii, 121; xiv, 476.)

The special application of this method to small quantities of blood when it is desired to determine the quantity of sugar present in the blood is described further on.

A similar method can be used, also, for the purifying of ferments. It has been shown, for example, that the protein can be removed from mixtures containing serum-albumin and invertin, leaving the invertin behind; in this case, the mixture is acidified and kaolin is used instead of dialyzed iron. (See L. Michaelis.)

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Rona* (P.) & *Michaelis* (L.).** *Weitere Beiträge zur Methodik der Enteiweissung. Biochem. Ztschr., Berlin,* ***1907, *v, 365–367.*

(d) *Total Non-protein Nitrogen*

In order to determine the amount of incoagulable nitrogen, or rest-nitrogen, present in the blood, the coagulable protein must be first removed. Several methods of removing protein from fluids are in vogue. Among these may be mentioned (1) precipitation with alcohol; (2) removal by means of kaolin, or colloidal hydroxid of iron (Rona and Michaelis, 1908—see above); (3) by the mastix method (Michaelis and Rona); (4) by precipitation with corrosive sublimate (Schenk, 1893).

For ordinary clinical purposes the following method, used by the assistants in the Baltimore Clinic, has sufficed:

(a) Add 5 c. c. of the blood to be tested to 75 c. c. of 95-per-cent alcohol and allow to stand for at least 12 hours.

(2) Filter, collecting the filtrate directly in a Kjeldahl flask, washing the precipitate several times with 95-per-cent alcohol.

(3) Drive off the alcohol by heating over a steam-bath.

(4) In the residue determine the nitrogen content by the Kjeldahl method.

(5) Calculate the grams of nitrogen per litre of blood serum.

Many workers now supplement this by a second precipitation of the alcoholic filtrate with zinc chlorid solution.

From now on, I think it better to remove the coagulable proteins by the use of dialyzed iron.

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Woods** (A. C.).* *Studies of the nitrogen partition in the blood and spinal fluid. Arch. Int. Med., Chicago,* ***1915, *xvi, 577–586.*

(*e*) *Ammonia-content of the Blood*

This is now best estimated by the colorimeter method of Folin and Denis (Jour. Biol. Chem., 1912, xi) with the aid of Nessler's solution and the Duboscq colorimeter.

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(*f*) *The Urea-content of the Blood* (*Marshall*)

By far the best method is that of E. K. Marshall. This depends upon the principle that the urea in the blood can be hydrolyzed by the urease of the Soja bean into ammonium carbonate and the amount of the latter determined by Folin's air-current method for ammonia.

The technic is simple:

(1) Two specimens of blood serum of 2 c. c. each are accurately measured into test tubes.

(2) To one of the tubes is added 1 c. c. of the Soja bean extract. The surface

of the serum in both tubes is covered with toluol to prevent putrefaction. The two tubes are placed in the thermostat at 37.5° C. for 2-6 hours. The ammonia-content of both specimens is then determined by Folin's air-current method, the ammonia being caught in $\frac{N}{50}$ HCl. (See Folin's method for estimating ammonia). The difference in ammonia-content between the two specimens represents the amount of ammonia that has resulted from the decomposition of the urea in the tube containing urease. The number of cubic centimeters of $\frac{N}{50}$ HCl neutralized by this ammonia, multiplied by 0.0006 gives the amount of urea in grams present in the specimen; or, multiplying by 0.00028, we get the amount of urea nitrogen from either of these volumes. The amount in grams per litre of serum can be easily calculated.

The Soja-bean, or Soy-bean, extract can be made by mixing 10.0 grams of powdered Soja beans with 100 c. c. of water, allowing it to stand, shaking frequently, for one hour. Then 10 c. c. of $\frac{N}{10}$ HCl are added and the whole allowed to stand 15 minutes longer. Filter and preserve under toluol. This solution keeps for from 5 to 6 days. Instead of this extract, the Soja bean powder (1.0) can be used. I advise strongly obtaining the active ferment in tablets from Hynson, Westcott & Co., Charles and Franklin Streets, Baltimore.

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(*g*) *Amino-nitrogen of the Blood*

This is best determined by Van Slyke's method, which makes use of the principle that aliphatic amino-groups react with nitrous acid to give off free nitrogen, both from the acid and from the amino-group, quantitatively. A known amount of nitrous acid is used, and, after the nitrogen has been evolved, the nitrous acid remaining undecomposed is absorbed by alkaline permanganate solution. The pure nitrogen is then measured and the amino-nitrogen value calculated from Van Slyke's tables.

The method is applied to blood in the following way:

(1) Mix 30-50 c. c. of blood with 9-10 times its volume of 95-per-cent alcohol, and record the volume of the mixture. Shake thoroughly, and allow to stand for 24 hours.

(2) Filter through a dry folded filter into a graduate, without washing the precipitate. Note the volume of the filtrate and work it up as an aliquot part of the blood-and-alcohol mixture.

(3) Concentrate *in vacuo,* or on the water-bath, to 3-5 c. c.

(4) Decompose the amino acids by Van Slyke's method. The decomposition of the amino acids is completed in 5 minutes at 15-20 degrees, in 4 minutes at 20 degrees, in 3½ minutes at 20-25 degrees, and in 2-3 minutes above 25 degrees.

(5) The gas is purified and measured in Van Slyke's apparatus. A correction can be made for urea. For full details, consult the original paper.

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(*h*) *Amino Acids of the Blood*

The work of isolating the individual acids of the blood has only just been begun. It is necessary, as yet, to convert them into difficultly-soluble derivatives, especially into β-naphthalin-sulpho derivatives, and the like (Fischer-Bergell).

It is to be hoped that, in experimental work on animals, the "artificial-kidney method," recently devised by J. J. Abel, may soon give us much new information concerning the content of the blood in the various individual amino-acids.

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(*i*) *Hippuric Acid of the Blood*

(1) Remove the protein of the blood by the method of Rona and Michaelis.

(2) Apply the method of Wichowski (described in Hofmeister's Beiträge, 1905, vii, 265) or the methods described in Kingsbury's article.

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(*j*) *Purin Bodies of the Blood*

i. Determination of the Total Purins

The method of K. Wiener permits of the determination of the free and combined purin bodies of the blood. For other methods see references.

ii. Determination of the Uric Acid of the Blood

Several methods have been recommended, but they may all be discarded in favor of the new method of Folin and Denis (Jour. Biol. Chem., 1913, xiii, 469). This is a colorimetric method with the use of a phospho-tungstate reagent.

(1) Collect 15-25 c.c. blood; mix with 0.1 gram powdered potassium oxalate, and pour the mixture into five times its weight of a boiling $\frac{N}{100}$ acetic-acid solution and filter.

(2) To the filtrate add 5 c.c. of 50-per-cent acetic acid, and concentrate the solution.

(3) To the concentrate, add five drops of 3-per-cent solution of silver lactate, two drops of magnesia mixture, and 10-15 drops of concentrated ammonia, and centrifugalize.

(4) Pour off the supernatant fluid, and to the residue add five drops of hydrogen sulphid water and one drop concentrated HCl; drive off the excess of H_2S by heating the centrifugalizing tube in boiling water.

(5) Centrifugalize again, and transfer the supernatant fluid to a graduated flask, and add to it 2 c.c. of the uric acid reagent (obtained by boiling 100.0 sodium tungstate with 80 c.c. of 85-per-cent phosphoric acid and 750 c.c. water, and bringing the mixture up to exactly one litre), and 10-20 c.c. saturated soda solution; then add water to make 25, 50 or 100 c.c.

(6) Compare the color, in a colorimeter, with that of a standard solution made by adding 0.001 grams of pure uric acid, 2 c.c. of uric acid reagent, and 20 c.c. of soda solution. One can use either the Duboscq colorimeter, or Autenrieth and Funk's colorimeter.

For the latter, a special wedge-tube has been prepared containing a permanent blue solution. In calibrating the wedge-tube, uric acid (0.01 per cent) is dissolved in 0.1-per-cent lithium carbonate solution; 1, 2, 3, . . . 10 c.c. of this uric acid solution is placed in a 50 c.c. graduate and to it are added 2 c.c. of the "uric acid reagent," 5 c.c. of saturated sodium carbonate solution; then water is added to the mark 50. After being shaken well, the mixture is allowed to stand for 15 minutes at the room temperature. Then the clear portion of the blue fluid is poured into the trog of the colorimeter, and one determines, in the ordinary way, by dislocation of the comparison wedge, the scale marks on the colorimeter at which the two solutions in the trog and in the wedge show the same tint. It is found that the amounts of uric acid given below correspond to the scale marks placed beneath them:

Milligrams uric acid	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8
Color equivalent on the scale..	90	80	70	59	50	40	29	19

With the help of this color-wedge, amounts of 0.1-0.8 mg. of uric acid can be determined. The readings are most accurate between the scale marks 80-30, that is for a uric-acid content of 0.2-0.7 mg.

For full directions for the determination of uric acid by means of this wedge in the Autenrieth-Königsberger colorimeter, see the article by Autenrieth and Funk (Münch. med. Wchnschr., 1914, lxi, 457). The method is applicable to the determination of uric acid in the blood, or in the urine.

The method of Folin and Denis is not yet wholly satisfactory but its originators are trying to improve it so that later we may have a still more reliable method.

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(*k*) *Bile-pigments of the Blood*

These are best determined by Hammarsten's method. (See his textbook.)

(*l*) *Indoxyl, Indol and Skatol of the Blood*

These are best determined by the method of Hervieux (Compt. rend. Soc. de biol., Paris, 1904, lvi, 622).

9. Studies of the Ferments and Antiferments in the Blood

During the last few years there has been an astonishing activity among workers who are interested in the investigation of the ferments and the antiferments in the blood. The technic of ferment investigation has grown with rapidity. The main facts are easily accessible in the monograph of Oppenheimer, and in that of Wohlgemuth, the references to which are given below.

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(*a*) *Ferments in the Blood Affecting Proteins*

i. The Coagulative Ferments

Thrombin and Prothrombin.—These are best determined by the method of Howell (Amer. Jour. Physiol., 1910, xxvi, 453; Arch. Int. Med., Chicago, 1914, xiii, 76. See also Whipple, Arch. Int. Med., Chicago, 1913, xii, 637).

Fibrinolytic Ferment.—Goodpasture's work on this ferment is referred to under "Hemorrhagic Diseases."

Lab-ferment.—(See Morgenroth, Centralbl. f. Bact., 1899, xxvi, 349.)

Precipitins.—(See Section on Infectious Diseases.)

ii. The Hydrolytic Ferments

Leukoprotease.—For determining the presence of this ferment, we use the method of Müller and Jochmann.

(1) On a Löffler serum plate, with smooth surface, place a drop of an emulsion of polymorphonuclear leukocytes, and, in order to avoid bacterial growth, place it in a thermostat at 50°-55° C.

(2) After a few hours, examine the surface of the plate; if proteolysis has occurred, it will be obvious as a little hollowed-out area, or dimple, at the site of the drop.

A drop of blood will react positively, if there be a large number of polynuclear leukocytes, or of myelocytes, in the blood (as in myelogenous leukemia); a drop of normal blood, or a drop of blood from a lymphatic leukemia, does not cause proteolysis.

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(*b*) *Ferments in the Blood Affecting Purins*

i. Nucleases

These split nucleinic acid into Levene's nucleotides and nucleosides, three ferments corresponding to the three stages. It is believed that *nuclease* and *nucleotidase* are secreted by the intestine, and that *nucleosidase* is found only within the cells.

To test for these ferments, a solution of alpha-thymo-nucleinate of sodium is used (see articles by F. Sachs, Ztschr. f. physiol. Chem., 1905, lvi, 337; by W. Jones, and by Levene). For references, See Part XIII.

ii. Desamidases

These include *guanase*, which transforms guainin into xanthin, and *adenase*, which transforms adenin into hypoxanthin. (See Walter Jones, "Nucleic Acids, Their Chemical Properties and Physiological Conduct," New York, 1914, 1-118.)

iii. Purin Oxidases

These include (1) *xanthin oxidase*, which transforms hypoxanthin into xanthin and xanthin into uric acid, and (2) *uricoxidase*, or so-called uricolytic ferment, which oxidizes uric acid. The latter ferment exists in many aminals but not in man.

The application of the study of these ferments to hematology has only just begun. We mention these studies since it is likely that, in the near future, they may loom larger than at present.

(*c*) *Ferments in the Blood Affecting Carbohydrates*

i. Diastase

Make a starch-paste plate (10 per cent), and place on it a droplet of an emulsion of leukocytes, or of blood rich in white cells. If diastase be present, amylolysis occurs, with formation of a dimple.

ii. Glycolytic Ferment

This ferment decomposes dextrose. It is very sensitive to acids and to alkalis. It can be demonstrated in blood by the method of P. Rona and Doeblin (Biochem. Ztschr., 1911, xxxii, 489).

(d) *Ferments in the Blood Affecting Fats*

i. Lipase

Wax Method.—(1) Make a plate of yellow wax (melting-point 63-64 degrees). (2) Place upon the plate a drop of blood, or of serum. If lipase be present, lipolysis will become obvious, through formation of a dimple (Bergell).

Monobutyrin Method (*Kastle; Hanriot*).

(1) Make a 1-per-cent solution of monobutyrin (ethyl butyrate) in water, shake vigorously, neutralize with dilute soda solution and filter.

(2) To 10.0 c.c. of the filtrate, add 3-4 c.c. of blood serum in each of two flasks, and keep for 24 hours in the thermostat. At the same time, make two control tests with boiled serum.

(3) Remove from the thermostat and to each flask add 50 c.c. of 90 per cent alcohol, 5 c.c. ether, and a few drops of phenolphthalein; titrate with $\frac{N}{10}$ NaOH until the first rose color appears. Average the results obtained from the two flasks, in each instance. Subtract the results obtained in the control flasks from the results obtained with the non-heated serum; this will give the amount of fat cleavage.

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(e) *Ferments in the Blood Affecting Tyrosin, Phenol, Guaiac and Hydrogen Peroxid*

i. Tyrosinase

This ferment has been found in man in melanotic tumors. It converts tyrosin into melanin and it converts adrenalin into a dark brown pigment. Its occurrence in the blood has not yet been demonstrated, but studies on the blood would seem worth while, in special cases. (For the methods of demonstrating it, see Brugsch and Schittenhelm, "Technik der Speziellen Untersuchungsmethoden," 1914, ii, 846.)

ii. Phenolase

This ferment oxidizes aromatic amines and phenols, giving rise to colored substances. It has been studied in the blood, and in the blood-building organs, by Winkler and by W. H. Schultze, who have made use of the so-called indophenyl-blue synthesis of Roehmann-Spitzer.

(1) Fix the blood smear, or the smear from the bone-marrow, in formol alcohol, and then immerse it for several minutes in each of the following solutions, successively:

(2) One-per-cent alkaline solution of alpha-naphthol (prepared by heating one part of *a*-naphthol in 100 parts water, adding drop by drop 1 c.c. KOH).

(3) One-per-cent aqueous solution of dimethyl-p-phenlylendiamin (Merck), which should be filtered before use.

(4) Transfer to distilled water. The specimen can then be examined directly under the microscope.

Polymorphonuclear leukocytes and myelocytes show a beautiful blue color in the protoplasm (granules), while the nuclei remain uncolored. The stain is durable for a half to one hour and can be kept in dry preparations still longer. Lymphocytes and certain young forms of myeloblasts do not yield the reaction. Large mononuclear and transitionals yield a positive reaction. None of the other cells of the body except the cells of the lacrymal and salivary glands yields the synthesis.

A modification of the method known as modification B, consists in mixing equal parts of a 2-per-cent solution β-naphtholnatrium (Merck's mikrozidin) and a 1-per-cent solution hydrochlorate of dimethyl-p-phenylendiamin. Filter. The granules stain green; in tap-water, the color changes to deep violet-black.

iii. Peroxidases

These ferments are capable of transferring oxygen, but only in the presence of hydrogen peroxid. We test for them by bringing the ferment-solution, in the presence of H_2O_2, in contact with some body that is easy to oxidize, such as guaiac, benzidin or leukomalachite green.

To apply this method to blood (Brandenburg), one dissolves a few drops of blood in 2-4 c. c. distilled water (to destroy the R. B. C.), and then pours cautiously upon it a layer of fresh 5-per-cent alcoholic tincture of guaiac, which contains some peroxid. If peroxydase be present, a deep blue ring will appear at the point of contact of the two fluids, the color soon changing to a dirty gray.

When the reaction is positive it is due to peroxydases arising from polymorphonuclear leukocytes, or myelocytes. It does not occur unless as many as 20,000 white cells per cubic millimeter are present. Lymphocytes do not contain this ferment.

For quantitative determinations of peroxydases see Kastle and Schedd (Amer. Chem. Jour., 1902, xxvi, 526), von Fuerth and Czylhartz (Hofmann's Beiträge, 1907, x, 358), and Kastle and Amoos (Bull. xxxi, Hygienic Laboratory, United States Public Health and Marine Hospital Service, 1906).

Smears of blood can be stained as follows (Kreibisch): Stain with solution (1- or 2-per-cent in distilled water) of benzidin-mono-sulphate of soda (obtainable from Adler of Karlsbad), to which is added a drop of a very dilute solution of H_2O_2 (2 drops of a 30-per-cent solution to 10 c. c. water). Counterstain, if desired, with Jenner's stain.

The reaction is positive in P. M. N., P. M. E., P. M. B., L. M., and T.; in M. and Mb.; but it is always negative in S. M. and Lb.

iv. Catalase

This ferment decomposes hydrogen peroxid into molecular oxygen and water. Its presence can be demonstrated by the method used in my wards by Winternitz, Henry and McPhedran:

(1) Collect 0.025 c. c of blood from the lobule of the ear with an especially graduated pipet.

(2) Dilute immediately with 10 c. c. distilled water, *i. e.*, a dilution of one part of blood to 400 parts of water.

(3) In each of two salt-mouth bottles (100 c. c.), place 5 c. c. of the diluted blood, using one bottle for the test and the other as a control.

(4) In one of the bottles, place a small vial containing 5 c.c. of commercial hydrogen peroxid (3 per cent), made neutral. Connect the bottle with a gas burette to collect the gas formed by the action of the catalase upon the hydrogen peroxid. Agitate for one minute, and make readings every 15 seconds.

In normal cases, there is a liberation of 14 to 17 c. c. of oxygen in 15 seconds. The amount liberated is constant, for each person, over long periods. In pathological states, there are variations in the total amount, or in the daily amounts. For the diagnostic value of this test, see the Introduction.

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(*f*) *Ferments in the Blood Affecting the Blood Corpuscles*

These include the iso-agglutinins and the isohemolysins that act upon the red corpuscles. The isohemolysins follow the same rules as the iso-agglutinins, so that we test only for the latter. (See above; Moss's Method for Testing for Iso-agglutinins.)

(*g*) *Ferments in the Blood Affecting Cells, and Products of Cells, Foreign to the Blood*

i. Bacterio-agglutinins; Bacteriolysins; Opsonins

These are probably of the character of ferments, though only the complement of the bacteriolysin is a ferment, since its amboceptor is thermostable. These ferments are described in the section on Infectious Diseases.

ii. Abderhalden's Defensive Ferments

These include the ferments against placental protein, against carcinoma protein, thyroprotein, etc. The method for testing for them has been described above under Abderhalden's Reaction (Dialysis Procedure; and Optic Method).

Reference

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(*h*) *Antiferments in the Blood*

i. Antithrombin

The blood may contain an excess or a deficit of antithrombin (Whipple). When antithrombin is in excess, grave hemorrhagic symptoms may develop (see articles by Howell, and by Whipple, referred to under Thrombin and Fibrinogen).

ii. Antitrypsin

Determination of the Antitrypsin Titer by the Method of Müller-Jochmann.—The blood serum to be tested is mixed in definite proportions with a solution of trypsin. A small drop of this mixture is placed upon a Löffler serum plate and allowed to act at 55-60 degrees. The formation of a dimple in the plate shows that tryptic digestion has occurred.

We next determine by mixing a definite amount of trypsin with increasing or diminishing amounts of blood serum, how much serum must be added in order just to inhibit the trypsin effect. Of course one must know the trypsin titer for normal serum.

Method of O. Gross.—As is well known, casein in alkaline solution is precipitated by acetic acid, while the digestive products of casein (caseoses) are not. In case all casein is digested, the addition of acetic acid no longer causes turbidity. One determines, simply, in what proportions trypsin and serum must be mixed in order that the trypsin effect upon casein is just inhibited. The titer for the serum under examination is compared with the titer of normal serum.

For the use of the antitrypsin reaction and the diagnosis of carcinoma, see Introduction.

iii. Anti-fibrinolytic Ferment

The occurrence of this antiferment in normal blood has been demonstrated. (See reference to Goodpasture's work, under Hemorrhagic Diseases.)

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10. Determination of the Carbohydrates and Acetone Bodies in the Blood

(*a*) *Glycogen in the Blood*

There is always a little glycogen in the white corpuscles; but, in order that it may be easily demonstrated, it must be present in pathological amounts. Such larger amounts occur especially in suppurations, when the glycogen can be demonstrated in the leukocytes and platelets by means of iodin.

The Iodin Reaction.—(1) Make a blood smear and dry it in the air in the ordinary way.

(2) Imbed it in a drop of the following mixture: Pure iodin 1.0, potassium iodid 3.0, distilled water 100.0, gum arabic q.s., to syrupy consistence.

In the leukocytes, and in the blood platelets, if glycogen be present, a diffuse brown discoloration appears, or brown granules become visible (*iodophilia*).

(*b*) *Dextrose in the Blood (Glucose)*

On account of the growing importance of studies on hyperglycemia, exact methods of estimating the sugar in the blood have become of importance clinically. Since the amount of dextrose present is always small, and since only small amounts of blood are usually available for examination, it has been necessary to devise especial methods for these exact determinations. The four best methods at present are: (1) the colorimetric method as modified by Forschbach and Severin; (2) the titration method of Bertrand as modified by Moeckel and Frank; (3) the rapid clinical test recently devised by Gitlow and Harowitz (1914); and (4) the method of Lewis and Benedict.

i. Colorimetric Method (Forschbach and Severin)

(1) With a pipet, place 5 c. c. of defibrinated blood in an especial Erlenmeyer flask, provided with a glass stopper, and which has been exactly weighed beforehand; determine the weight of the blood added.

(2) Remove the protein (method of Rona and Michaelis), by adding 35 c. c. of dialyzed iron (liquor ferri oxydati dialysati, Merck) and 10 c. c. of a cold saturated solution of sodium sulphate. This brings the volume of the fluid to exactly 50 c. c. Shake immediately, but for only a short time, and filter through a Nutsche.

After 10 or 20 minutes there will be obtained 30-35 c. c. of a colorless filtrate, free from protein and from iron.

(3) According to the content of the blood in sugar, place from 5-30 c. c. of this filtrate in an Erlenmeyer flask containing 5 grams potassium carbonate (C. P.) and 4 grams potassium sulphocyanate (C. P.), dilute with water to 35 c.c., and then add 100 c.c. of Bang's copper solution (160 g. $KHCO_3$, 100 g. K_2CO_3, 66 g. KCl, and 100 c. c. 4.4 per cent $CuSO_4$, 5 H_2O, in one liter of water), and boil for 3 minutes.

(4) Cool immediately, and wash the fluid out into a 50 c.c. graduated flask, quantitatively, by means of a 10-per-cent calcium-carbonate calcium-sulphocyanate solution, filling up exactly to the 50 c.c. mark. Compare the color with a freshly prepared test-solution, without addition of sugar, in Plesch's chromo-photometer, or in the wedge-tube apparatus designed for hemoglobin estimations of Autenrieth and Königsberger, and calculate the result from the accompanying table.

Thickness of layer of test Solution in Millimeters	Dextrose content of the Reduced Solution in Milligrams			Thickness of layer of test Solution in Millimeters	Dextrose content of the Reduced Solution in Milligrams		
	10 c.c. Bang sol.	5 c.c. Bang sol.	2 c.c. Bang sol.		10 c.c. Bang sol.	5 c.c. Bang sol.	2 c.c. Bang sol.
19.5	0.25	0.125	0.050	15.2	3.11	1.550	0.622
19.1	0.50	0.250	0.100	15.1	3.17	1.585	0.634
18.6	1.00	0.500	0.200	15.0	3.22	1.610	0.644
18.5	1.06	0.530	0.212	14.9	3.28	1.640	0.656
18.4	1.12	0.560	0.224	14.8	3.33	1.665	0.666
18.3	1.17	0.585	0.234	14.7	3.39	1.695	0.678
18.2	1.23	0.615	0.246	14.6	3.44	1.720	0.688
18.1	1.29	0.645	0.258	14.5	3.45	1.725	0.690
18.0	1.35	0.675	0.270	14.4	3.50	1.750	0.700
17.9	1.41	0.705	0.282	14.3	3.55	1.775	0.710
17.8	1.46	0.730	0.292	14.2	3.60	1.800	0.720
17.7	1.52	0.760	0.304	14.1	3.65	1.825	0.730
17.6	1.58	0.790	0.316	14.0	3.70	1.850	0.740
17.5	1.64	0.820	0.328	13.9	3.75	1.875	0.750
17.4	1.70	0.850	0.340	13.8	3.81	1.905	0.762
17.3	1.75	0.875	0.350	13.7	3.87	1.935	0.774
17.2	1.81	0.905	0.362	13.6	3.94	1.970	0.788
17.1	1.87	0.935	0.374	13.5	4.00	2.000	0.800
17.0	1.93	0.965	0.386	13.4	4.06	2.030	0.812
16.9	2.00	1.000	0.400	13.3	4.11	2.055	0.822
16.8	2.06	1.030	0.412	13.2	4.17	2.085	0.834
16.7	2.11	1.055	0.422	13.1	4.22	2.110	0.844
16.6	2.17	1.085	0.434	13.0	4.28	2.140	0.856
16.5	2.22	1.110	0.444	12.9	4.33	2.165	0.866
16.4	2.28	1.140	0.456	12.8	4.39	2.195	0.878
16.3	2.33	1.165	0.466	12.7	4.44	2.220	0.888
16.2	2.39	1.195	0.478	12.6	4.50	2.250	0.900
16.1	2.44	1.220	0.488	12.5	4.56	2.280	0.912
15.0	2.50	1.250	0.500	12.4	4.63	2.312	0.926
15.9	2.57	1.285	0.514	12.3	4.69	2.345	0.938
15.8	2.64	1.320	0.528	12.2	4.75	2.375	0.950
15.7	2.71	1.355	0.542	12.1	4.81	2.405	0.962
15.6	2.79	1.395	0.558	12.0	4.88	2.440	0.976
15.5	2.86	1.430	0.572	11.9	4.94	2.470	0.988
15.4	2.93	1.465	0.586	11.8	5.00	2.500	1.000
15.3	3.00	1.500	0.600	....	....	.....	.....

The whole procedure can be carried through in 20 to 30 minutes. If one use only 2.5-3.0 c.c. of blood, one uses 5 c.c. of Bang's solution; if 1-1.5 c.c. of blood are used, only 2 c.c. of Bang's solution are required; of course, in the end-calculations, the results are correspondingly reduced.

ii. Method of Moeckel and Frank

These authors remove the protein with dialyzed iron, and then determine the sugar by Bertrand's method. The results are very accurate even with small amounts of blood. (See Ztschr. f. physiol. Chem., lxv and lxix.)

The sugar-content of the plasma lies between 0.07 and 0.11 per cent, that of the whole blood usually between 0.065 and 0.095 per cent. Since there are often differences between the content of the total blood and that of the plasma in sugar, it is, in general, preferable to make a sugar estimation on the plasma, rather than on the whole blood, since it is the plasma that is predominantly concerned in carbohydrate metabolism.

iii. Method of Lewis and Benedict

This is the method the use of which I advise. These authors dilute 2 c. c. of blood with 8 c. c. of water and 15 c. c. of concentrated picric acid solution. The proteins of the blood become precipitated and are filtered out. To 8 c. c. of the filtrate are added 2 c. c. of concentrated picric-acid solution and 1 c. c. of 10-per-cent sodium-carbonate solution; the mixture is evaporated over a free flame in a Jena test tube to small volume, or until a precipitate forms. A little water is now added and the solution brought to the boiling point; the fluid is then transferred to a 10 c. c. measuring flask, water added to make up the volume, and the solution filtered and compared in a Duboscq colorimeter with a standard picramic-acid solution that is so prepared as to correspond in color to that produced by 0.64 mg. of dextrose under the conditions above described.

R. G. Pearce shortens the time required in using this method by heating the tubes in an autoclave under a pressure of 2.5 kg. per sq. cm. for 15 to 30 minute periods. A large number of specimens may be tested at one time. As his procedure does not entail any evaporation, he found it convenient to use 6 c. c. of the filtrate in place of 8 c. c. After the autoclaving, he brings the solutions up to 10 c. c. in a measuring flask and compares them with the standard. These solutions show 75 per cent of the sugar contained in the tubes made up with 8 c. c. of the blood-filtrate. He finds that the standard solution of picramic acid used by Benedict and Lewis may be diluted one fourth, and the readings may then be made direct.

For a method of rapidly determining the value of the solution in terms of sugar, Pearce makes use of curves plotted on millimeter paper, which are very convenient (see his article).

According to Lewis and Benedict, the blood-sugar content of healthy persons varies between 0.09 and 0.11 per cent (average = 0.1 per cent).

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(c) *Acetone in the Blood*

i. Method of Embden and Kalberlah

(1) Dilute 100 c.c. of blood with 4-5 times its volume of 1-2 per cent solution of primary potassium phosphate.

(2) Distill off from the mixture (cooling well) about 100 c.c.

(3) Acidulate the distillate with H_2SO_4, and again subject to distillation, allowing $\frac{1}{4}$ or $\frac{1}{5}$ to distill over.

(4) In the latter distillate, determine the acetone according to the method of Messinger-Huppert (conversion of the acetone in alkaline solution by iodin and iodid of potassium into iodoform, titrating back the excess of iodin with thiosulphate.

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(d) *β-oxybutyric Acid in the Blood*

This is best determined by Geelmuyden's method. (See Ztschr. f. physiol. Chem., 1908-9, lviii, 256.) This acid is, of course, a fatty acid but is considered here because of its relation to acetone.

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11. Determination of the Fats and Fatty Acids in the Blood

In outspoken lipemia, the presence of fat can be recognized by the naked eye examination of the serum, or, in smaller amounts, on microscopic examination, or on centrifugalization in a hematocrit. If one collect the blood in capillary tubes and leave them lying in a horizontal position, the fat collects in the uppermost layer and can be extracted by ether.

For exact studies of the fat in the blood, blood plasma, or blood serum, we resort to alcoholic extraction with subsequent saponification of the alcoholic extract by the method of Kumagawa-Suto (Biochem. Ztschr., 1908, viii, 218).

(a) *Study of Fats by Method of Kumagawa-Suto*

(1) Collect 10-30 c.c. of blood and mix with 3-5 times its volume of absolute alcohol. Allow this to stand over night, filter through a Nutsche, and wash repeatedly. Extract the residue in a hot extractor with absolute alcohol 3-5 hours over the flame. Add this alcoholic extract to the alcoholic filtrate already obtained.

(2) To the total alcohol extract, add 7-8 c.c. saturated NaOH (sp. gr. 1.5) and saponify on the water-bath for a half to one hour.

(3) After evaporation of the alcohol, dissolve the residue in a little warm water, place in a separating funnel, and shake thoroughly with hydrochloric acid; then proceed by Kumagawa-Suto's method (ether and petroleum-ether extraction). After this the cholesterin is separated from the neutral fats. (See original article.)

(*b*) *Study of Fats after Extraction*

When the fats have been separated, their exact study requires:

(1) The determination of the melting-point.

(2) The determination of the acid number (number of milligrams of KOH necessary to neutralize the fatty acids contained in one gram of fat).

(3) The determination of the saponification number (number of milligrams of KOH uniting with the fatty acids arising on the saponification of one gram of fat).

(4) The iodin number (the percentage of iodin bound by a given amount of fat). This is a measure of the content in unsaturated fatty acids.

(5) The Reichert-Meissel number (amount of volatile fatty acids contained in five grams fat).

(6) Acetyl number (number of oxy-fatty acids, alcohols, and other constituents containing OH groups).

For the technic of these various procedures, the handbooks of organic and industrial chemistry may be consulted.

The determination of the iodin number has been used by Eppinger, King and Medak for the determination of the unsaturated fatty acids in the blood in anemias, before and after splenectomy. (See Eppinger, Berl. klin. Wchnschr., 1913, i, 1509; 1572.)

(*c*) *Lactic Acid in the Blood*

This is best determined by the method of Peritz and Glikin. (See Ztschr. f. exp. Pathol. u. Therap., 1910, viii, 255.)

(*d*) *Cholesterin in the Blood*

This can be determined by the method of Kumagawa-Suto already mentioned, or more simply by the colorimetric method of Autenrieth and Funk. (See Münch. med. Wchnschr., 1913, 1243.)

Cholesterin is really a secondary alcohol, but it is usually studied with the fats.

References

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12. Determination of the Inorganic Constituents of the Blood

(*a*) *Total Ash of the Blood*

For this purpose, the methods described by H. Aron in the article "Aschenanalyse," in the Handbuch der biochemischen Arbeitsmethoden (Abderhalden), 1909, i, 372-428, should be followed.

(*b*) *Calcium and Magnesium of the Blood*

McCallum has demonstrated a diminution of the lime salts in the blood in tetany. (Jour. Exp. Med., xi, 118.) The importance of an adequate calcium content for proper coagulation has long been known. For methods, see Aron's article.

(*c*) *Potassium and Sodium of the Blood*

See Aron's article. Also, Federer, Ztschr. f. physiol. Chem., 1914, lxxxix, 232.

(*d*) *Chlorids of the Blood*

i. von Hoesslin's Method

(1) Dilute 5 c.c. of serum with distilled water.
(2) Add a little HNO_3 and filter.
(3) Titrate by Volhard's method with ammonium sulpho-cyanid (see Urine).

ii. Rojee and Fritsch's Method

(1) Weigh exactly, about 10 c.c. blood in a 250 c.c. flask, and dilute with 150 c.c. distilled water.

(2) Add 50 c.c. (exactly) liquor ferri oxydati dialysati (Merck), and 5 c.c. of a 20-per-cent solution $MgSO_4$. Add water to exactly 250 c.c., and shake violently for several seconds. Allow to stand a few minutes and filter, through a folded paper-filter, into a dry flask.

(3) In exactly 100 c.c. of the water-colored filtrate, determine the chlorids, by Mohr's method, with $\frac{N}{10}$ silver nitrate solution, using neutral potassium chromate as indicator.

(4) Make a "blind experiment," without blood, and subtract the number of c.c. of silver solution used from the amount used in the actual experiment.

iii. Micro-estimation of NaCl

By the method of Bang (Biochem. Ztschr., 1913, xlix, 34), the amount of NaCl in as little as 100 milligrams of blood can be determined.

(iv) Chloridometry in Small Amounts of Blood According to McLean and Van Slyke

Principle.—The protein is removed, and the chlorides are titrated in the protein-free filtrate with a silver-nitrate solution, the excess of silver being titrated back, using a delicate indicator, with a solution of potassium iodide.

Removal of the Proteins.—This is best done by coagulation. Two cubic centimeters of the fluid to be tested (oxalated blood-plasma; urine exudate) are drawn into a 2 c.c. pipet that has been calibrated to contain 2 + or — 0.005 c.c. From the pipet, the fluid is transferred quantitatively to a 20 c.c. stoppered volumetric flask, which contains 10 c.c. of a 10-per-cent solution of magnesium sulphate. The pipet is rinsed twice by drawing up into it the solution from the flask. Two drops of acetic acid (50 per cent) are added, and distilled water to the 20 c.c. mark. The fluids are mixed by inversion of the stoppered flask, and heated in a steam bath to 100° for 10 minutes. Evaporation is prevented by keeping the stopper loosely in place, and on cooling the contents return to their original volume. The proteins are coagulated and the chlorids distributed evenly between the fluid and the precipitated albumin.

After cooling, the contents of the flask are poured on about 0.3 gms.

blood charcoal (Merck's "Blood Charcoal, Reagent," purified by acid and free from chloride is essential) in a small beaker and mixed. A few minutes later, the liquid is filtered through a dry folded filter, and a water-clear filtrate obtained. Should a little charcoal pass through at first, the early part of the filtrate should be poured back into the same filter, when it will pass through again colorless.

Titration of the Protein-free Filtrate.—The chlorides are now precipitated with $AgNO_3$ in the presence of HNO_3, the AgCl removed by filtration, and the excess silver titrated back with KI with nitrous acid and starch as indicator (end-point blue).

Solutions:

I. *The Silver-nitrate solution.* This is an acid M/29.25 solution of silver nitrate, 1 c.c. of which is equivalent to 2 mg. of NaCl.

$AgNO_3$	5.812 gm.
HNO_3 (Sp. Gr. 1.42)	250 c.c.
Water to	1,000 c.c.

II. *The potassium-iodide solution.* This is a solution of M/58.5 potassium iodide, 1 c.c. of which is equivalent to 1 mg. of NaCl.

KI	3.0 gm.
Water to	1,000 c.c.

The solution is standardized against the silver solution by adding 5 c.c. of the latter to 5 c.c of solution III (see below) and titrating with the iodide solution to the blue end-point. The iodide solution is then diluted so that 10 c.c are exactly equivalent to 5 c.c of the silver solution.

III. *The sodium citrate, sodium nitrate and starch solution.*

Sodium citrate ($Na_3C_6H_5O_7+5\frac{1}{2}H_2O$)	446.0 gm.
Sodium nitrate	20.0 gm.
Soluble starch	2.5 gm.
Water to	1,000.0 c.c.

The starch is dissolved by heating with 500 c.c. of water. The salts are added, and the mixture heated until all are dissolved. Filter while hot through cotton. Wash filter with hot water; cool filtrate and make up to 1,000 c.c. The solution keeps indefinitely. If it become cloudy on standing, its efficacy is not impaired.

The Titration.—The titration is done in a *certified* 25 c.c. graduated cylinder into which the 10 c.c. of the protein-free filtrate are placed, 5 c.c. of the acidified $\frac{M}{29.25}$ silver nitrate solution (=solution I) added, and the whole made up to the 25 c.c. mark with water. [In case the fil-

trate contains more than 10 mg. of NaCl, a smaller quantity of the filtrate must be used.]

Two drops of octyl (caprylic) alcohol are added, the vessel stoppered, and the whole mixed well by inversion several times. Precipitation is immediate. After 5 minutes, the solution is filtered (clear) through a dry folded filter.

An aliquot part of the filtrate—20 c.c.—is next taken with a pipet for titration. Just before titration with Solution II, one volume of Solution III is added equal to the volume of Solution I represented in the filtrate to be titrated. A slight turbidity appears. Solution II is then run in from a buret to the end-point—the first definite blue color. The result may be calculated from the following formula:

$$\text{Grams NaCl per liter} = \frac{12.5\ (8 - \text{c.c. KI solution used})}{\text{c.c. of protein-free filtrate.}}$$

The method is very accurate; the error is much less than 1 per cent of the chlorids in the original 2 c.c. of fluid tested.

(e) *Iron of the Blood*

The colorimetric method of determining iron in the blood has already been described. (See Hemoglobin Estimations.)

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E. Methods of Examining the Hematopoietic Organs

1. Examination of the Bone-marrow

If we except the tenderness of flat bones, especially of the sternum, on percussion, in anemic states, the bone-marrow is not directly accessible to clinical examination, and we have to form deductions regarding the pathological changes going on in it from examinations of the blood (white and red corpuscles) and occasionally of the urine (presence or absence of Bence-Jones body).

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2. Examination of the Lymph Glands

(*a*) *Inspection and Palpation of the Lymph Glands*

The lymph glands are much more accessible to clinical examination. The normal lymph glands are scarcely palpable, but in disease they will become very much enlarged so that they are not only palpable, but also visible as masses in the subcutaneous tissues. They should be systematically examined in groups, and for each group one must keep in mind the territory from which the lymph is derived. If the lymph glands be enlarged, the size and consistence should be carefully determined, and it should be noted whether the enlarged glands are discrete, or are matted together. Irregularity of the surface may be important. Tuberculous lymph glands often contain areas softer than others; in neoplastic lymph glands, hard, irregular nodules may be palpable.

(*b*) *Exploratory Puncture of Lymph Glands*

Swollen lymph glands may be punctured and fluid be withdrawn from them by a hypodermic needle and examined for cells, bacteria and parasites. This method has proven very fruitful in the demonstration of the presence of trypanosomes in the sleeping sickness of Africa (Todd). It may also clear up the diagnosis in pyogenic infections, in tuberculous abscess, in lues, or in bubonic plague.

(*c*) *Excision of a Lymph Gland for Histological, or Bacteriological Diagnosis*

This method is particularly valuable for differential diagnosis of glandular diseases in the neck. A gland may easily be removed under cocain anesthesia, and one portion of it used for cultures (Rosenow's method) and for smears, another portion of it for animal inoculation, and a third portion after fixation in formol, sectioning, and staining, for histological examination. A diagnosis may by this means often be made certain when otherwise it could at best be probable. Among the causes of general glandular enlargement are: (1) syphilis; (2) leukemia; (3) tuberculosis; local or regional glandular enlargements are found in connection with various local infections (arthritis, tuberculosis, lues, ulcus mollis, bubonic plague, Hodgkin's disease), and, also, with carcinoma, or, less often, sarcoma, in neighboring organs.

Subcutaneous enlargements resembling lymph nodules may be met with in chronic pyemic processes, and especially in blastomyces infections. Here attempts at excision for diagnosis reveal the presence of pus and on microscopical examination bacteria or fungi may be found.

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3. Examination of the Spleen

The methods of examining the spleen include inspection, palpation, percussion, x-ray examination, and (rarely) exploratory puncture.

(*a*) *Inspection and Palpation of the Spleen*

Only when the spleen is greatly enlarged, as in cases of myeloid leukemia, does the tumor become visible on inspection of the abdomen. It may

then cause bulging of the left side of the abdomen and enlargement of the lower aperture of the thorax on the left.

The most practical method of examination of the spleen is by bimanual palpation, the physician to the right of the couch and the patient lying, part way turned over upon his right side (diagonal position). Normally, the organ is not palpable, and if the edge can be felt, it means, either that the spleen is out of position, or that it is enlarged.

To palpate the spleen, the right hand is placed flat upon the abdomen, the finger-tips lying just below the margin of the ribs, in the left hypochondrium. The left hand lifts the patient's lower thorax on the left from below, and the patient is told to take a deep breath. The mass formed by an enlarged spleen moves up and down with the movements of respiration. If the spleen be enlarged, the anterior pole will be felt to pass under the fingers as a smooth round body. In some instances the spleen is felt best as it emerges during inspiration; in other instances, one gets it best as it recedes during expiration. If the enlargement be greater, the anterior edge can easily be felt and sometimes a *notch* on the medial edge. Sometimes the spleen is so large that it may descend into the pelvis and its medial edge may even cross over the middle line to the right side of the body. I have seen cases in which more than half the abdominal cavity was occupied by an enormous spleen. In such cases, we note whether the surface of the spleen is smooth, or rough, and nodular, and irregular, and whether fluctuation can be felt in it. Occasionally a friction fremitus can be felt over the spleen in perisplenitis.

On palpation, we detect not only enlargement of the spleen, but also alterations in its consistence. It is usually soft in typhoid fever, firmer in malaria, and very hard in leukemia, in Banti's disease, in chronic inflammations, in venous stasis, and in neoplasms.

(*b*) *Percussion of the Spleen*

On percussion, the normal splenic dullness extends from the 9th to the 11th rib on the left side. It does not pass further forward than the costo-articular line (line joining the left sternoclavicular joint with the tip of the 10th rib); it emerges behind with the dullness over the kidney and spine. The area of dullness in the mid-axillary line amounts to 5-7 cm. If the colon be filled with feces, or the stomach be much distended with gas, the percussion of the spleen yields unsatisfactory results. Percussion is, for obvious reasons, often misleading in pulmonary emphysema, in meteorism, and in ascites.

Enlargement of the Spleen.—This is met with in (a) many infectious diseases (typhoid, malaria, typhus, relapsing fever, sepsis, occasionally, in pneumonia); (b) in chronic passive congestion, portal or general (thrombosis of the splenic or of the portal vein, cirrhosis of the liver, cardiac

decompensation); and (c) in diseases of the blood, and of the blood-making organs (the leukemias and pseudoleukemias, Banti's disease, etc.).

When the spleen is much enlarged, the colon lies behind it, a point that helps to differentiate enlargement of the spleen from a large mass due to the kidney.

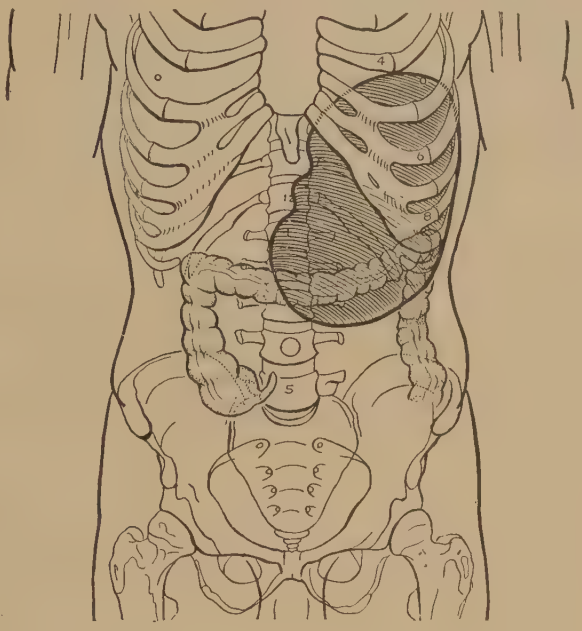

Fig. 312.—Diagram Illustrating Position of a Splenic Tumor.

(c) *Exploratory Puncture of the Spleen*

One resorts to exploratory puncture of the spleen only rarely, though the blood thus obtained may show malarial parasites or Leishman-Donovan bodies when they cannot be found in the peripheral blood. Death has more than once occurred from splenic puncture made for diagnostic purposes, due to tearing of the distended capsule and hemorrhage into the peritoneal cavity. If puncture is done, the patient should be warned to hold his breath during the operation. During my period as pathological anatomist, I had occasion to observe, at autopsy, a rent in the spleen, which had caused death from hemorrhage into the peritoneal cavity; a good internist had made an exploratory puncture to establish the diagnosis of malaria, and the patient, contrary to definite warning, had taken, suddenly, a deep inspiration, at the moment the needle was introduced.

In tropical splenomegaly, the diagnosis is often made by means of splenic puncture, smears of the splenic juice being thus obtained, dried, and stained by Leishman's method, when the Leishman-Donovan bodies can be seen in the cells. Splenic puncture is rarely required for diagnosis. I advise against resorting to it unless under exceptional and urgent indication.

SECTION II

SPECIAL DIAGNOSIS OF THE PRINCIPAL DISEASES OF THE BLOOD AND OF THE HEMATOPOIETIC ORGANS

Only the more important conditions can be referred to. In some of them, the blood itself is markedly changed, along with changes in the blood-building organs; in others, very marked changes occur in the blood-building organs without marked concomitant blood-changes. The leucocytoses and leucopenias have already been considered. We shall take up here:

1. The anemic or erythropenic states.
2. The erythrocytoses and the erythremic states.
3. The leukemic states.
4. The pseudoleukemias and other leukemoid states.
5. Diseases characterized by disturbances in the coagulability of the blood (the hemorrhagic diseases).
6. Disorders (other than the hemolytic anemias) in which hemolytic phenomena are dominant.
7. The diseases of the spleen.

A. The Anemias or Erythropenias

1. Classifications of the Anemias

Great difficulty is encountered in satisfactorily classifying the anemias, owing to the fact that the etiology of many forms is but poorly, or not at all, understood.

(*a*) *Primary and Secondary Anemias*

A common clinical classification has been the division into (1) primary or idiopathic anemias, and (2) secondary anemias. By a primary anemia

was meant a genuine disease of the blood itself; by a secondary anemia, an alteration in the blood consequent upon a disease of some organ or due to some known etiological factor. Thus, the Addison-Biermer type, or so-called pernicious anemia, and chlorosis, were placed among the primary anemias; most other anemias were regarded as secondary. But, in the last analysis, there is no such thing as a primary anemia. Every anemia must be secondary to some deleterious influence, for the blood is not an organ, but the product of many organs, predominantly of the bone-marrow and of the lymphadenoid tissues as far as its cells are concerned. The red blood-corpuscles do not multiply in the blood itself.

(*b*) *Anemias in Which the Blood Formation is of Post-Embryonal Type and Those in Which it is of Embryonal Type*

The next step forward in the classification of the anemias was made by Ehrlich, on the basis of the regenerative forms that appear in the blood. The red corpuscles of postembryonic life are derived from the normoblasts of the bone-marrow, while those of early embryonic life are derived from larger cells—the so-called megaloblasts. Ehrlich's studies showed that in some anemias the regenerative form is predominantly normoblastic, in others, predominantly megaloblastic; thus, in the posthemorrhagic anemias and in chlorosis, no megaloblasts are seen; but, if erythroblasts appear in the blood, they are of the type of normoblasts. On the other hand, in pernicious anemia, and in the anemia pseudoleukemica infantum, the predominant erythroblast in the blood is a megaloblast. Accordingly, the anemias were subdivided by Ehrlich into:

(1) Anemias of postembryonal blood-formation type, and
(2) Anemias with embryonal blood-formation type.

It was believed, at that time, that the prognosis in the latter is always bad.

More recent studies, however, indicate that a certain number of megaloblasts may occur in almost any kind of anemia, even in the posthemorrhagic anemias. Moreover, intermediate forms between normoblasts and megaloblasts are frequently seen in the blood, both in human anemias, and in the anemias of experimental animals; and some anemias in which megaloblasts, to a certain extent, appear, are curable.

As Morawitz emphasizes, a classification of the anemias on the ground of the regeneration types seen in them is not a very happy one, for (1) the embryonal and the postembryonal regeneration types cannot be sharply separated from one another, transitions existing between the two; (2) the megaloblastic type is not an expression of a specific toxic effect, but occurs in the most different conditions; and (3) in itself, it has nothing "pernicious" about it, but, on the contrary, seems to represent, really, a

favorable form of reaction of the hematopoietic organs. The conditions that determine the appearance of megaloblasts in the blood include (1) the age of the person affected; the younger the patient, the more likely is the megaloblastic reaction to appear; (2) the intensity of the erythropoietic stimulus, the megaloblastic reaction occurring only with intense stimuli; (3) the disintegration of red blood-corpuscles within the body, it having been shown that regenerative processes are more intense in the marrow when the anemia is of the sort in which red blood-corpuscles undergo disintegration inside the body itself, rather than in anemia in which the blood is simply lost from the body by hemorrhage. This difference may depend upon the retention of the formative material within the body, or upon specific stimulation of some sort; we do not know. Certain it is that megaloblasts are more common in the hemolytic types of anemia than in any other form, and, on this account, an enumeration of the megaloblasts and of the normoblasts, respectively, is often of help in the differential diagnosis of the different forms of anemia.

(*c*) *Anemias Classified According to Pathogenetic and Etiological Differences*

With Pappenheim, Masing and Morawitz, I am inclined to attempt a classification of the anemias based upon a general pathogenetic and etiological point of view. This attempt is surrounded with peculiar difficulties, owing to the fact that the etiology of many forms of anemia is but poorly understood, and the etiology of the Addison-Biermer type and of some other types is entirely unknown. Though Hunter of London has done much to increase our knowledge of the severe anemias, the etiology and pathogenesis is not so simple as one might be inclined to believe from a perusal of his publications. Any classification must at present be tentative, and subject to change as our knowledge of the anemias grows.

Morawitz's main subdivision into (1) anemias due to temporary or more permanent increase in the amount of blood destroyed, and (2) anemias dependent upon decreased blood formation, must appeal to everyone. I shall adopt it as the basis of the classification used in this treatise, though, in the further subdivision of the anemias, it will be seen that my classification differs somewhat from that of Morawitz. The classification which I, for the present, adopt is as follows:

I. **Anemias due to hemorrhage, or to increased blood destruction.**
   - (1) Anemias due to hemorrhage (the posthemorrhagic anemias).
     - (a) Acute posthemorrhagic anemia.
     - (b) Chronic posthemorrhagic anemia.
   - (2) Anemias due to increased blood destruction (the hemolytic anemias).

(a) Hemolytic anemias of unknown etiology.
  (i) Acute form with leukocytosis.
  (ii) Chronic type (Addison-Biermer anemia).
(b) Dibothriocephalus anemia.
(c) Hemolytic anemias occurring in lues, in carcinoma, and in the puerperium.
(d) Hemolytic anemias due to known chemical substances (potassium chlorate, phenylhydrazin, nitrobenzol, etc.).
(e) Anemia pseudoleukemica infantum.
(f) Congenital and familial hemolytic jaundice.

II. **Anemias due to defective or to decreased blood formation.**

(1) Chlorosis.
(2) Anemias accompanying tumors or sclerosis of the bone-marrow (the myelopathic anemias).
(3) Anemias accompanying hypoplasia of the bone-marrow.
  (a) In states of inanition and cachexia.
  (b) In conditions of unknown origin (aplastic, or aregeneratory, anemia).

In the *posthemorrhagic anemias*, there is, nearly always, a low color-index, the bone-marrow being unable to compensate for the loss of hemoglobin as rapidly as for the loss of red corpuscles. When hemorrhages are often repeated and long continued, the time will come when the bone-marrow can no longer respond to regenerative stimuli. When such a time arrives, the anemia will no longer be an anemia wholly due to loss of blood, but will in part depend upon insufficient blood formation (Morawitz and Blumenthal).

The term *hemolytic anemia* is used to include not only the cases in which hemolysis occurs in the circulating blood but also the conditions in which there is increased blood destruction in the spleen and liver, owing to the circulation of some poison in the blood that increases, in some way, the vulnerability of the red corpuscles and leads to their phagocytosis in the blood-destroying organs. A well-known example, which may be cited, is the effect of phenylhydrazin, or of pyrodin, upon the hemoglobin of the red blood-corpuscles; in experimental anemias due to poisons, there is no hemoglobinuria, or only rarely, for the hemoglobin does not seem to be set free in the blood; on the contrary, erythrocytes are injured, and are rapidly removed from the circulating blood, being caught up by the phagocytes, especially by those of the splenic pulp. If injuries, such as those that give rise to the hemolytic anemias, persist for a long time, we may not only have increased blood destruction, but, after a period of accelerated hematopoiesis, the bone-marrow may gradually become exhausted and erythroblasts will begin to disappear from the blood. In

such cases, the hemolytic anemia becomes complicated by an anemia due to decreased blood formation. It is, however, surprising to find how far the body can go in its regenerative activity; in the severe hemolytic anemias, the red marrow, instead of being limited to the few bones in which it normally exists, encroaches widely upon, and largely replaces, the yellow marrow of the long bones.

In the hemolytic anemias, besides the evidence of erythropenia, we have hints of increased blood destruction in (1) the subicteric tint of the skin and mucous membranes, (2) the dark color of the urine, and (3) urobilinuria (Syllaba), though these are not constantly present. At autopsy, large amounts of hemosiderin, evidently derived from the disintegrated corpuscles, are found stored up, especially in the liver (Hunter, Quincke).

It has been maintained by some that the anemias here designated as hemolytic, represent, in reality, a primary disease of the bone-marrow, this organ giving rise in such states to red corpuscles of less than normal resistance. While this possibility must be granted, it seems very probable, from what we know of the experimental anemias and of the di-bothriocephalus anemia, that in the hemolytic anemias we have, in reality, to deal with the circulation of toxic substances in the blood, and that these injure normal corpuscles rather than that corpuscles of low resistance are formed and succumb abnormally easily to the ordinary wear and tear of life.

It will be noted that the *Addison-Biermer type of anemia* is included among the hemolytic anemias as a chronic form of unknown etiology. The term "progressive pernicious anemia" has been used in the bibliography to include not only this Addison-Biermer type, but also di-bothriocephalus anemia and certain other forms of curable anemia. Common to them all is the high color-index and the presence of megaloblasts and macrocytes in the blood. It seems, however, especially important to separate the Addison-Biermer type with its malign prognosis, from the curable forms of hemolytic anemia with their benign prognoses. It will be seen that the curable forms are those in which the etiology is known, and in which the cause can be removed. It may be that we shall some time discover the cause of the Addison-Biermer type. Let us hope that this cause, when found, may prove to be a removable one.

It will be noted that, with Morawitz, I do not group the so-called *aplastic*, or *aregeneratory anemia* with the Addison-Biermer type at all. It would seem to be an anemia primarily due to an incapacity on the part of the bone-marrow to manufacture the red cells, while the Addison-Biermer is an anemia due to increased blood destruction, and in it the bone-marrow seems to possess exceptional powers of regenerative activity, at any rate for a long time.

In the great group of *anemias due to a defective or decreased blood*

formation, the defect may lie chiefly in an inability to produce hemoglobin, as in chlorosis, or in an inability to build red corpuscles, as in aplastic anemia, some myelopathic anemias, and the anemias following prolonged inanition or cachexia. In these cases the blood picture differs strikingly from that seen in the hemolytic anemias, since signs of regenerative activity (erythroblasts, polychromasia, basophilic granulation of the red cells) are largely, or entirely, absent from the blood.

Morawitz gives *chlorosis* a separate place, since in his opinion, it is less the blood picture than the total clinical symptom-complex that separates chlorosis from other forms of anemia. It seems to be convenient, however, to put it among the anemias due to defective blood formation.

Clinically, one can usually quickly *differentiate* between anemias due to increased blood destruction and those due to decreased blood formation, by the appearance of erythroblasts and other signs of regenerative activity (polychromasia, anisocytosis) in the peripheral blood in the former. This criterion, however, will not always suffice, since in the posthemorrhagic anemias there may be only a few erythroblasts in the blood, and, moreover, in the hemolytic anemias the nucleated red cells may be present in large numbers only at times of the so-called blood-crises.

In the anemias due to decreased blood formation, erythroblasts and polychromasic cells are only rarely found. Of course, a tumor destroying a large part of the bone-marrow may now and then excite a localized area of the marrow to increased activity, when, temporarily, nucleated reds may appear in the blood; but in such cases, as Morawitz emphasizes, the correct diagnosis can usually be made from the other symptoms.

It is not surprising that, when there are marked disturbances of erythropoiesis, there should also be some disturbance of leukopoiesis. As might be expected, the signs of increased leukopoiesis are more marked in the posthemorrhagic and in the acute hemolytic anemias than in the anemias due to defective blood formation. As signs of such accelerated leukopoiesis, there is often an outspoken leukocytosis and sometimes a few myelocytes go over into the blood. Occasionally, in tumors irritating the bone-marrow, a great many myelocytes may appear in the blood, giving rise to the so-called "irritation myelocytosis," in which the blood picture may suggest a combination of an anemia with a leukemia. In the chronic hemolytic anemias, and in the aplastic anemias, there is a diminished myeloid leukopoiesis, with diminution of the granular cells of the blood, a total leukopenia, and, accordingly, a relative lymphocytosis. It seems probable that the leukopenia that sometimes accompanies the Addison-Biermer type is due to a complicating depression of the bone-marrow function. Obviously, careful differential counts of the leukocytes in the blood may, along with the red count, the color-index, and the study of the stained red corpuscles, be very helpful in the differential diagnosis of the different forms of anemia.

2. Anemias Due to Hemorrhage or to Increased Blood Destruction

i. Anemias Due to Hemorrhage

(*a*) *The Posthemorrhagic Anemias*

In these anemias, the number of red blood-corpuscles is diminished. The hemoglobin is diminished in even greater degree, so that the color-index is low. There is often an accompanying leukocytosis of the neutrophilic type in the acute forms; and there may be a leukocytosis of the eosinophilic type in the chronic forms, due to uncinariasis or to other forms of helminthiasis. There is but little anisocytosis, though there may be some poikilocytosis in the severer cases. Regeneration forms occur, but usually in small numbers, and the erythroblasts are of the normoblastic type. The water-content of the blood is often temporarily increased. The platelets may often become increased, especially soon after a hemorrhage, and the coagulation time is shortened.

i. Acute Posthemorrhagic Anemias

Definition.—These are the anemias that follow the sudden loss of a large amount of blood. An adult will usually die if he lose more than half his blood; a child, after a loss of much less blood. In adults, therefore, a hemorrhage amounting to two liters must be considered very grave.

Symptoms.—If the hemorrhage prove fatal, death seems most often to be due to asphyxiation from insufficient oxygen (functional effect), though it is not always easy to distinguish between the symptoms due to loss of oxygen and those dependent upon insufficient filling of the vascular system and the fall of the arterial pressure (mechanical effects).

The mechanical effects can, of course, be overcome by intravenous infusions of salt solution, the functional effects, at least temporarily, by a direct or indirect transfusion of blood.

In non-fatal cases, attempts at regeneration quickly appear. The blood restores its water-content most quickly, and, next, the protein-content of the plasma. The regeneration of red corpuscles goes on more slowly, and the rebuilding of hemoglobin more slowly still.

The above facts explain why we have successively in the blood-picture, a hydremia, a leukocytosis, an oligocythemia, and an oligochromemia, these defects disappearing during convalescence in the order named.

Loss of blood is a powerful stimulus to the regenerative activity of the bone-marrow. Accelerated erythropoiesis leads to the regeneration of the red corpuscles and the hemoglobin; accelerated leukopoiesis leads to regeneration of the white cells. These are sometimes reproduced, at first,

in excess, and a neutrophylic leukocytosis is one of the most constant of posthemorrhagic phenomena. A few myelocytes may also go over into the circulating blood at such a time.

The length of time required to restore the blood to normal varies with the size of the hemorrhage, the age of the patient, his state of nutrition, etc. Usually, several weeks are necessary for complete recovery.

As a rule, only a few normoblasts go over into the blood, but many polychromasic red cells are visible for some time after the hemorrhage. The blood platelets are increased in number, and the coagulation time is shortened.

The neutrophilic leukocytosis and the normoblastemia soon disappear. The color-index remains low for some time.

ii. Chronic Posthemorrhagic Anemia

Definition.—These are the anemias that follow upon repeated small hemorrhages, occurring over a considerable period.

Symptoms.—The symptoms vary much in the different cases, depending upon the size, frequency, and localization of the hemorrhages, and the duration of the cause. The clinical picture varies according to whether the blood is lost from the body (external hemorrhage), or the hemorrhage takes place inside the body (*e. g.,* in the intestinal canal), so that the hemoglobin can be reabsorbed and used for the manufacture of new corpuscles. In the latter case, the color-index is not so low, and basophilic granulation of red cells is more outspoken than in cases of recurring external hemorrhage.

Etiology.—(a) Hemorrhages from mucous membranes (ulcus ventriculi, ulcus duodeni, hemorrhoids, recurring epistaxis, menorrhagia); (b) helminthiasis (hook-worm disease, bilharziosis); (c) amebiasis (amebic dysentery); (d) hemorrhages in diseases associated with hemorrhagic diathesis (scorbutus, hemophilia, etc.).

In the Southern United States, and in Porto Rico, posthemorrhagic anemia due to uncinariasis is very common. In the Johns Hopkins Hospital, we received formerly many of these cases from the Carolinas and Georgia, and we also have manifold opportunity of becoming acquainted with the anemia secondary to amebic dysentery.

In these cases of posthemorrhagic anemia due to animal parasites, the clue to the etiology lies (1) in the accompanying eosinophilia, and (2) the finding of the parasites (worms, amebae) on microscopical examination of the feces.

The di-bothriocephalus anemia (*q. v.*) is not a posthemorrhagic anemia, but a hemolytic anemia.

Blood Findings.—These resemble those of acute posthemorrhagic anemia, but the diminution in red cells and the loss of hemoglobin, occur-

ring gradually, may reach a much lower level without causing death. The hemoglobin may fall as low as 20-25 per cent, and the red cells to 1,000,000 or lower. Normoblasts and poikilocytes appear in the blood, in these graver cases, in considerable numbers; polychromasic red corpuscles are common, and there may be some anisocytosis, a few microcytes and macrocytes appearing in the blood; an occasional megaloblast may be seen. As a rule, there is a slight leukocytosis.

Diagnosis.—This is usually easy, if the whole state of the patient be considered, and a systematic examination of the blood and of the feces (occult blood, parasites) be made.

The severer forms might be mistaken for an Addison-Biermer anemia, but only on superficial examination. The low color-index, the discovery of the etiological factor, the predominance of normoblasts over megaloblasts in the blood, the low grade of anisocytosis, the pallor of the urine, the absence of the straw-colored tint, exclude an Addison-Biermer anemia. Now and then, a case may be seen in which the color-index is rather high, and the discovery of the etiological factor difficult. In such cases the diagnosis may for a time be in doubt.

(*b*) *Anemias Due to Increased Blood Destruction*

(*The Hemolytic Anemias*)

This group, as we have seen, includes all the cases that were formerly described as pernicious anemia, except the group of aplastic anemias. It includes, therefore, not only (a) the genuine Addison-Biermer type and (b) the acute types of unknown etiology, but also (c) the hemolytic anemias in which the etiology is known (see below).

i. Chronic Hemolytic Anemia of Unknown Etiology

(*Addison-Biermer Type of Anemia*)

If the term progressive pernicious anemia is to be used at all, it should include this group and also the aplastic group of anemias. The general tendency at present is to give up entirely the use of the term "pernicious anemia," since its sole criterion is perniciousness, and when this criterion is used as a basis for nosological grouping, it leads, as we have seen, to the inclusion under one heading of diseases that are entirely different from one another when viewed pathogenetically. I must agree, therefore, with William Hunter, Morawitz, O. Naegeli and others who recommend that we discard the term progressive pernicious anemia altogether.

There can be no doubt that, among the cases studied by Addison, Biermer and the clinicians who succeeded them, a number of different diseases were grouped together. Gradually, however, the etiology of several of these diseases has been discovered, and this has led to their removal

from the larger group. We now reserve the term Addison's anemia, or Biermer's anemia, for cases of chronic hemolytic anemia in which on systematic examination we can discover no cause, even at autopsy. The blood picture, however, is in no way different from that of the chronic hemolytic anemias of discoverable etiology. The diagnosis, therefore, depends upon (1) the demonstration of the presence of the blood picture characteristic of chronic hemolytic anemia, and (2) the exclusion of any etiological factor, in the present state of our knowledge, discoverable.

Criteria That Permit the Diagnosis of Chronic Hemolytic Anemia.—These include (1) The characteristic blood findings (marked anisocytosis and poikilocytosis; high color-index; the presence of megaloblasts; basophilic granulation of the red corpuscles; and leucopenia, with relative lymphocytosis).

(2) The insidious onset, with weakness without apparent cause.

(3) The characteristic course, with high-colored urine, urobilinuria, fever, straw-yellow tint to the skin and mucous membranes, gastro-intestinal disturbances, and nervous symptoms.

In excluding the hemolytic anemias of discoverable etiology, we systematically rule out (1) di-bothriocephalus anemia, (2) lues, (3) carcinoma, (4) the puerperium, and (5) chemical poisoning with $KClO_3$, pyrodin, phenylhydrazin, nitro-benzol, etc.

I emphasize this limitation of the term Addison-Biermer anemia at the beginning, for it is of the greatest importance not to confuse this progressive and fatal type with the other forms of chronic hemolytic anemia, since the former, in my experience, is sooner or later invariably fatal, and the latter are almost invariably curable, provided the etiology be discovered and the cause be removable.

Theories as to Etiology.—We may as well admit that we are absolutely ignorant as to the cause of this disease. We do know (1) that it is uncommon before middle life and in later life, the majority of the cases occurring in middle-aged people; (2) that well-to-do people are affected almost as often as the poor; (3) that, in certain instances, the disease occurs in families; (4) that it is distributed all over the world; and (5) that men and women are almost equally affected.

In the European bibliography, it is generally stated that women are more often affected than men, almost twice as often; Lazarus among 274 cases states that 102 were in men and 172 in women. In my personal experience, many more men than women have been affected, and this agrees with the experience of Osler, who states that the disease is twice as common in males as in females.

Pathogenesis.—One thing seems clear; the disease is due to increased blood destruction. Some noxa must enter or be formed in the body; this injures the red corpuscles and leads to their premature removal from the

blood. We come to this conclusion on account of what we know of the similar hemolytic anemias due to dibothriocephalus and to pyridin poisoning. But where does this noxa, or hemolysin, arise? Various theories have been advanced, some blaming the gastro-intestinal tract (Grawitz, W. Hunter), either the mouth (stomatitis, glossitis), the stomach (achylia gastrica), or the intestine (auto-intoxication). Extracts of the gastric and intestinal mucous membranes from patients dead of this anemia are said to be more hemolytic than extracts of normal mucous membranes (Berger and Tsuchiya); it has also been assumed that the increased hemolysis is due to the presence of an excess of oleic-acid esters and similar lipoids. Recently, the theory that in this disease the hemolysins originate in the spleen has been made the basis of the experimental treatment by splenectomy.

Let me emphasize again that the nature of the hemolysins, and the place of their origin, in the Addison-Biermer type, are as yet entirely unknown.

Symptoms.—The subjective complaints are not dissimilar to those in other forms of anemia (weakness, fatigability, headache, dyspnea, dizziness, ringing in the ears, palpitation). There is usually marked anorexia, and often constipation or diarrhea; meteorism and eructations are also often complained of. The patient gradually grows pale, and the skin assumes a lemon-yellow tint. It is surprising, however, how long a patient, owing to the gradual onset of the anemia and the tolerance acquired to it, can keep up his occupation before consulting a physician. One may, on the very first examination, find the blood count below 2,000,000. A sudden disturbance of vision, due to retinal hemorrhage, may first bring the patient to his doctor. Most often, however, it is progressive weakness that leads to consultation.

The patients are usually apathetic; the mentality becomes slowed.

On physical examination the pallor of the skin and mucous membranes and the lemon-yellow tint are so striking that one may suspect the condition when the patient enters the consulting room. This appearance of the skin and mucous membranes is very different from the waxy pallor of the young chlorotic, and from the gray pallor of carcinoma cachexia.

In this anemia, the patients do not look cachectic; indeed, they are often plump rather than thin. The ankles may be a little edematous. Petechiae and ecchymoses are common, as in all severe anemias. Pigmentation is rare.

Palpitation and dyspnea are often troublesome symptoms. Anemic murmurs may be audible over the heart and a *bruit de diable* is sometimes audible over the bulb of the jugular vein. The cases are sometimes diagnosed, erroneously, as subacute infective endocarditis.

On examination of the stomach-juice, there is always achlorhydria, and often complete achylia gastrica. Since dyspeptic symptoms commonly

accompany the condition, it is no wonder that the diagnosis of carcinoma ventriculi is often erroneously made. The intestinal disturbances may be very troublesome. I have seen several patients who suffered from periodic crises of abdominal pain that excited the suspicion of the existence of some surgical abdominal condition. The liver may be enlarged and firm, a sign that, together with the icterus, sometimes leads to an erroneous diagnosis of primary hepatic disease. The spleen is, as a rule, not palpable, though in the cases that are operated upon, or that come to autopsy, the spleen may be found somewhat enlarged, which does not surprise us when we consider the increased blood destruction. The urine is nearly always high-colored, and its urobilin-content is large. There may be albuminuria, but other renal symptoms are uncommon.

Examinations with the Zuntz-Geppert apparatus show no marked disturbance of gas metabolism, despite the high grade of anemia. It is probable that an accelerated circulation of the blood compensates for the oligemia and the oligocythemia.

Fever is present, at least in most cases. It is rarely high, and the chart is very irregular. Its cause is unknown. It may contribute to misleading the clinician into diagnosing an ulcerative endocarditis, or an obscure tuberculosis.

Symptoms referable to the spinal cord are not uncommon. Many of my patients complained of tingling in the hands and feet as an early symptom, and anesthesias, ataxias and spastic paraplegias are by no means uncommon. Frank Billings, in this country, has carefully described these anemic cord disturbances (see Combined Sclerosis, in section on Diseases of the Nervous System). In the severer cases, the clinical picture may resemble either that of a tabes dorsalis, or that of a spastic paraplegia, according as, respectively, the posterior funiculi, or the lateral funiculi, predominantly suffer.

Remissions.—One of the most remarkable features of the disease is the tendency to remissions either spontaneously, or under careful treatment (rest in bed, hydrochloric acid, arsenic, intestinal lavage, etc.). The patients may improve rapidly. They often think that they are cured, and return to their occupations for a longer or shorter period, but the symptoms, in my experience, inevitably recur. A patient may have two or three such remissions before entering upon his terminal attack.

Duration.—The disease is of variable duration. In some cases death occurs in a few months; as a rule it is postponed for from one to three years after onset. Now and then a patient lives much longer. Whether actual cure ever occurs is still doubtful.

Summary of Blood Findings in the Addison-Biermer Type of Anemia.

The Red Blood-corpuscles.—The number may be very low; when the anemia is outspoken the number is usually below 2,000,000. It may fall as low as 143,000 per c.mm. (Quincke), or as low as 138,000 (Naegeli). I have, myself, seen several cases where the blood count fell below 500,000.

In the fresh blood slide, one is struck at once by (1) the outspoken anisocytosis, usually more than 25 per cent of the erythrocytes being macrocytes, and (2) the high grade of poikilocytosis. Another feature in the fresh blood slide is the good color of most of the individual red cells, in marked contrast with the pallor of the cells in chlorosis and in the secondary anemias.

In stained preparations, a good many of the erythrocytes are polychromasic, and basophilic granulation is very common. There are nearly always nucleated red corpuscles in the blood, and, at times of blood crises, these may be present in very large numbers. Both normoblasts, with dark pyknotic nuclei, and megaloblasts, the latter often predominating, are present. Among the latter, enormous examples (gigantoblasts) are sometimes seen.

It must be remembered, however, that in this anemia there are sometimes periods when signs of regeneration temporarily disappear from the blood. The absence of nucleated reds, of polychromasic cells and of basophilic granulation, on a single examination, does not necessarily exclude the Addison-Biermer type.

Hemoglobin-content.—This is always diminished, but usually not to so great an extent as the red corpuscles.

Color-index.—This is, accordingly, usually high, nearly always more than 1, and often higher than 1.5. It is one of the most important signs of a chronic hemolytic anemia. There may be periods, however, in which the color-index is not over 1, or in which it may a little less than 1.

The White Blood-cells.—As a rule there is a moderate leukopenia, due to diminution of the white cells of myeloid origin, especially of the polymorphonuclear neutrophils, though the eosinophils and the large mononuclears are also diminished. The absolute number of the cells of lymphadenoid origin is usually not decreased, and they show, accordingly, a relative increase, sometimes making up half, or more than half, of the total white count.

The Blood Platelets are usually diminished in number.

Other Blood-findings.—The total amount of blood is usually diminished. The coagulation time is usually lengthened. The water-content of the blood is increased. The viscosity is low. The specific gravity is low, and may fall below 1,040. Most of these signs are due to the diminution in the number of the blood corpuscles, since the protein-content of the plasma may be normal.

Differential Diagnosis.—The diagnosis should not be difficult if what has been said regarding (1) the blood findings of chronic hemolytic anemia, (2) the anamnesis and the course of the disease, and (3) the absence of discoverable etiology, be considered. It is important not to depend on any one of these three factors alone, in making a diagnosis.

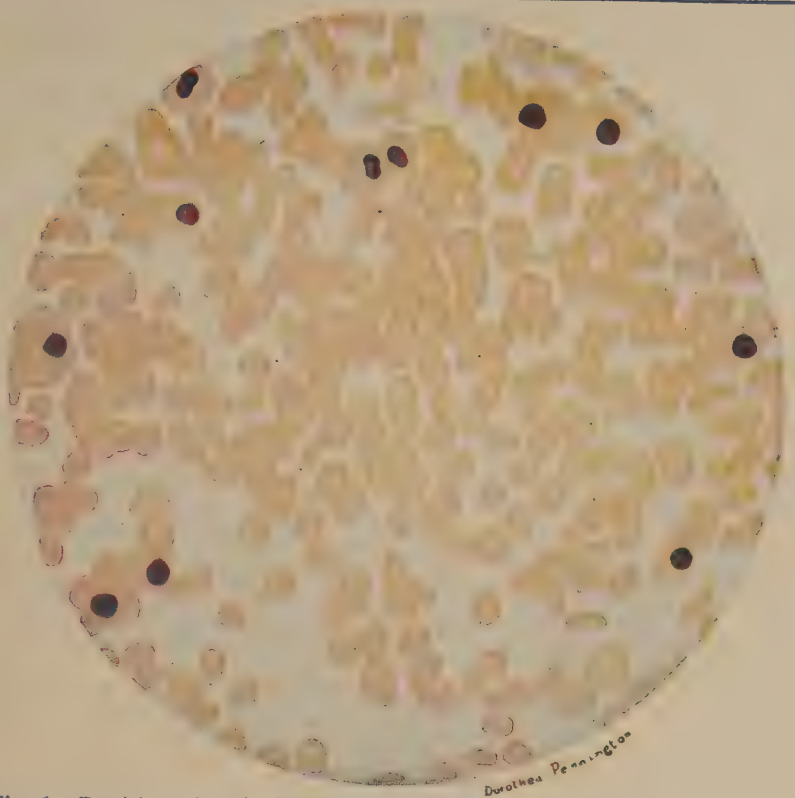

Fig. 1.—Pernicious Anemia Showing Normoblastic Crisis. Wilson Stain. × 360. (Original Drawing.)

Fig. 2.—Pernicious Anemia Showing Marked Anisocytosis and Poikilocytosis, Diffuse Basophilia, Megaloblast, Fragmentation of Nucleus, and So-called Extrusion of Nucleus. × 800. Wilson Stain. (Original Drawing.)

We differentiate the Addison-Biermer type of anemia (1) from *other chronic forms of hemolytic anemia* (discoverable etiology, anamnesis); (2) from *acute hemolytic anemias* (blood findings, including leukocytosis; course); (3) from *anemia pseudoleukemica infantum* (youth splenomegaly); (4) from *carcinosis of the bone-marrow* (physical examination, myelocytosis); (5) from *posthemorrhagic anemias and chlorosis* (history, low color-index, normoblasts, leukocytosis); (6) from *aplastic anemia* (absence of nucleated reds, of polychromasic corpuscles and of basophilic granulation of red cells from the blood, on *repeated* examinations); (7) from *subacute infective endocarditis* (blood culture, blood findings); (8) from *hepatopathies* (blood findings, history); (9) from *carcinoma ventriculi* (motility tests, x-rays, blood findings).

ii. Acute Hemolytic Anemia of Unknown Etiology (Leukanemia)

This condition was first described by Leube and Arneth, who designated the disease "leukanemia," since they thought it represented a combination of leukemia with the Addison-Biermer type of anemia. There were macrocytes and megaloblasts in the blood, in addition to a neutrophilic leukocytosis and a moderate grade of myelocytosis; the disease ran the course of an acute infection and terminated fatally.

The term leukanemia was badly chosen, since at autopsy no signs of leukemic proliferation were found. It is advisable to drop altogether the use of the term leukanemia, as no condition has yet been discovered that really represents a combination of leukemia with the Addison-Biermer anemia. Some of the cases are instances of the Addisonian anemia, some are instances of acute leukemia.

iii. Dibothriocephalus Anemia

Definition.—An anemia presenting, clinically, the symptoms and the blood findings of a chronic hemolytic anemia very similar to the Addison-Biermer type, but associated with presence of the large fish-tapeworm, dibothriocephalus latus, in the intestine.

Course.—The disease is common in Finland, and in other countries in which fresh-water fish are much eaten. Most of our knowledge of this anemia is due to the investigations of Finnish observers (Tallqvist, Schapiro, Schauman).

Pathogenesis.—The mere presence of the dibothriocephalus in the intestine does not cause this type of anemia. It is only when parts of the worm, or whole worms, undergo disintegration within the intestine that the anemia develops. It would seem that, during such disintegration, specific hemolytic poisons are set free and are absorbed. On timely expulsion of the worm, cure results, but, if the disease has lasted too long, cure does not follow expulsion.

The nature of the hemolytic substance has been disputed. According to Tallqvist and Faust, it is a lipoid, namely, the cholesterin ester of oleic acid. Apparently, individual predisposition plays a part. Other tapeworms rarely, if ever, give rise to this type of anemia, though in two cases invasion of the intestine by Tenia saginata is said to have caused such an anemia, cure resulting in both instances after expulsion of the tapeworm (Reckzeh, Naegeli).

Diagnosis.—This depends on (1) the blood findings of chronic hemolytic anemia, and (2) the discovery of the etiology (ova, or proglottides, in the feces).

iv. Other Chronic Hemolytic Anemias

Chronic Hemolytic Anemia in Lues.—This is undoubtedly rare, though cases have been reported (F. Müller, O. Naegeli). One must always keep in mind the possibility of the accidental concomitance of an Addison-Biermer anemia and a luetic infection. If the Wassermann reaction be positive, however, one should never neglect a thorough salvarsan therapy, especially as the administration of salvarsan is one of the best forms of arsenical therapy, even in ordinary Addison-Biermer anemia (Boggs).

Chronic Hemolytic Anemia Due to Carcinoma.—The majority of anemias secondary to carcinoma are not of the chronic hemolytic type. They take as a rule, the form either of a chronic posthemorrhagic anemia or of an inanition anemia, and they usually show a low color-index, very few nucleated red corpuscles, and especially few megaloblasts or none, and often a leukocytosis. In a few instances, however, a true chronic hemolytic anemia, indistiguishable, as far as the blood findings are concerned, from that met with in the Addison-Biermer type, has been described in association with carcinoma ventriculi (Cabot, von Noorden). It seems to me probable that, in these cases, as Naegeli suggests, there was an accidental concomitance, rather than a causal relationship.

Chronic Hemolytic Anemia in Pregnancy and in the Puerperal Period.—This also is exceedingly rare. Most of the anemias, so described, have been posthemorrhagic anemias. Undoubtedly, however, a true chronic hemolytic anemia may occur in this association. It is not unlikely that, in certain women, hemolysins of fetal or placental origin develop during pregnancy, just as, in certain other women, a pernicious form of intoxication occurs in pregnancy and causes the so-called pernicious vomiting of pregnancy (Whitridge Williams). It would seem that the prognosis is good if the pregnancy be interrupted, or if the patient does not die before normal term has been completed.

Chronic Hemolytic Anemias Due to Chemical Intoxications.—In experimental animals, typical hemolytic anemia can be produced by poisoning with pyridin, phenylhydrazin, etc. There is, at first, a leukocytosis, but it is followed later by a leukopenia, and, sometimes, by the typical blood-picture of an Addison-Biermer anemia.

Among such anemias in human beings, that occurring in lead-poisoning may be of this type, though the anemia of lead-poisoning rarely reaches a high grade. The anemia of nitro-benzol poisoning described by Ehrlich may also belong to this type. The anemia of benzol poisoning, studied carefully by Selling in my clinic, is probably not a hemolytic anemia, but rather an anemia due to decreased blood formation, since the benzol has a specific destructive effect, first upon the leukopoietic tissue, and later upon the erythropoietic tissue of the bone-marrow.

Anemia pseudoleukemica infantum.—I include this disease under the hemolytic anemias because the majority of cases would appear to belong to this type, though undoubtedly some of the cases reported can scarcely be regarded as hemolytic anemias. It is necessary to emphasize that anemia pseudoleukemica infantum is not a unity, but includes anemias of different sorts, just as did the "pernicious anemias" of older writers.

This disease, first described by von Jaksch and Hayem, is a severe anemia of gradual onset and may be of long duration.

Blood Findings in Anemia pseudoleukemica infantum.—*The Red Blood-corpuscles.*—These may be markedly diminished in number

(usually, to a count of from one to two millions). In the fresh blood, there is moderate to marked anisocytosis. In stained specimens, nucleated red corpuscles are usually present in enormous numbers and there is usually a predominance of megaloblasts. Polychromasic red corpuscles are very common, as are also basophilic granulations of the red corpuscles.

Hemoglobin Content.—This is markedly lowered, but usually not to so great a degree as the number of red cells.

Color-index.—This is, accordingly, usually above 1.

The White Blood-corpuscles.—Their behavior is variable. Usually there is a leukocytosis of neutrophilic type, often marked (20,000 W. B. C. or more), thus differentiating the disease, strikingly, from the Addison-Biermer anemia of adults, and causing it to approach more closely to the acute hemolytic anemia of known etiology (or leukanemia of Leube). Myelocytes often appear in the blood along with this neutrophilic leukocytosis, a finding that has erroneously led many clinicians to make the diagnosis of myeloid leukemia in children so affected. One should always remember that, in children, the appearance of myelocytes in the blood is a common accompaniment of any condition in which the bone-marrow is stimulated to accelerated activity. In a few cases, the lymphocytes have been absolutely increased in number, indicating an accelerated lymphadenoid leukopoiesis in addition to the increase in myeloid leukopoiesis.

At autopsy, extensive hyperplasia of both the erythropoietic and the leukopoietic tissue of the bone-marrow has been found, as well as myeloid metaplasia in other organs (spleen, liver, lymph glands). The yellow marrow of the long bones is often converted into red marrow. No leukemic changes have been found.

The prognosis in anemia pseudoleukemica infantum is often good, though some of the cases, despite careful treatment, terminate fatally.

For a full analysis of the literature of the subject, the collective review of Flesch may be consulted.

3. Anemia Due to Defective or to Decreased Blood Formation

(*a*) *Chlorosis*

Definition.—This is a disease, especially of young women, affecting them in a characteristic way. There are (1) peculiar changes in the blood, including (a) a marked diminution of the hemoglobin-content, with relatively slight diminution in the number of red blood-cells per cubic millimeter, and, accordingly, a low color-index, with no signs, or very few signs, of an accelerated erythropoiesis, and with undisturbed leucopoiesis, (b) a polyplasmia, or serous plethora, without hydremia, and

(c) an increase of the blood platelets; and (2) a host of other symptoms, especially subjective symptoms, not due directly to the anemia, but rather to disturbances of chemical and nervous correlations, probably dependent upon an as-yet-unexplained endocrinopathy.

The administration of iron acts as a specific in curing the disease, at least in the majority of cases.

Etiology.—The cause of this disease is unknown. It is very common, though physicians see less of it now than formerly, since the department stores have begun to sell Blaud's pills.

It is more common in some families than in others, but usually occurs sporadically. It affects young women after the age of puberty, most often between the 20th and the 25th year of life. Only 2 of 242 cases began after the 24th year (von Noorden), though if it be once established earlier, there may be recurrences, even after the 30th year. Chlorosis does not occur before puberty, and it does not occur in the male sex. It seems likely that the cases reported as chlorosis in the male have been other forms of anemia.

A change in the external circumstances of life has frequently been noted as preceding the onset of chlorotic phenomena. In Germany, especial emphasis has been laid upon the frequency of the development of chlorosis in servant-girls on leaving country life to take up a position in the city. The disease is by no means confined, however, to the working-classes, but is common also among the well-to-do and leisure-classes. Whether the wearing of corsets and gastroptosis is responsible in any of the cases, seems very doubtful. The theory that unsatisfied sexual desire plays an important part in the etiology of chlorosis does not, in my opinion, have much basis, though it is a striking fact that marriage, and especially the bearing of children, is often associated with the disappearance of chlorotic symptoms in those affected.

Symptoms.—Aside from the symptoms that accompany all forms of anemia (weakness, vertigo, headache, dizziness, ringing in the ears, black spots before the eyes, dyspnea on exertion, palpitation), chlorotic patients often present symptoms usually described as "hysterical." They are pathologically irritable, capricious, and have weeping-spells. The appetite is poor, and the patients often desire unusual foods, especially sour foods (pickles). As in pregnant women, there may be perversion of the appearance of chlorotic symptoms in those affected.

Gastro-intestinal symptoms are common (distention, eructation, colicky pains, constipation). The patients complain of feeling cold, or state that their hands and feet are cold while the head is hot and congested. Many patients keep up their daily occupations, but go about them in a "draggy" sort of way. Other patients are so exhausted that they become incapable of work and take to their beds.

On examination, the waxy pallor of the skin and mucous membranes

is striking. The patients are usually well nourished; indeed, they may be fat, but they have a pasty, almost edematous, look about the face and beneath the eyes, and there may be actual edema of the feet and ankles. Occasionally, the pallor is masked by vasomotor dilatation in the cheeks. My first teacher of internal medicine, Professor McPhedran of Toronto, always emphasized the importance of suspecting anemia in young women who had especially red cheeks. If the conjunctivae and tongue of such red-cheeked girls be examined, the pallor is usually evident. The skin never shows the lemon-yellow tint so characteristic of the Addison-Biermer type of anemia. There are often dark rings about the eyes, and occasionally a greenish appearance is seen; to this, the disease owes its name, but the symptom is certainly not commonly present.

Anemic murmurs are audible over the heart, and there may be dilatation of both sides of the heart. A *bruit du diable* can be heard in the veins of the neck; it is very loud when the patient sits or stands; one listens with the stethoscope placed just above the sternoclavicular joint, over the bulb of the jugular vein.

Chlorotic patients seem to be occasionally subject to infectious phlebitis with thrombosis. These thrombi are most common in the veins of the lower extremity. Occasionally, thrombosis of the venous sinuses of the brain occurs and ends fatally; fortunately, it is a very rare complication.

Another complication of chlorosis, much more common, is ulcus ventriculi.

Constipation is usually a striking feature. Some authors attribute the disease to intestinal auto-intoxication dependent upon the constipation. The spleen is sometimes enlarged and palpable, though by no means constantly.

Amenorrhea is almost a constant accompaniment; it may be the first symptom complained of. Other patients suffer from menorrhagia, dysmenorrhea, or leukorrhea.

The urine is pale, and there may be moderate polyuria. The urobilin-content is not higher than normal, but rather lower, indicating the absence of increased hemolysis.

The nervous symptoms are almost as constant as the blood findings in chlorosis (see above). In some cases, edema of the optic disk and edema of the retina have been observed; it has even been suggested that the nervous phenomena of chlorosis may depend upon a low grade of cerebral edema.

Summary of the Blood Findings in Chlorosis.—The Red Blood-corpuscles.—The number is, as a rule, somewhat diminished in the severer cases, but in mild cases the red blood-count may be normal. On the average, however, the number varies between three and four millions per cubic millimeter. There is no decrease in the number of red blood-corpuscles in the total amount of blood, even when the number in the unit

of volume is less than normal, since there is a marked increase in the total amount of blood in the body in chlorosis.

In the fresh blood, the pallor of the individual corpuscles is very striking. There is often some anisocytosis, and, in severe cases, this and poikilocytosis may be marked. If macrocytes are present, they are easily distinguishable from those of the chronic hemolytic anemias by their pallor.

Only in the severer forms are nucleated red corpuscles seen. When present, they are always, or practically always, normoblasts. Polychromasic red cells are usually present, but basophilic granulation of the red blood-corpuscles is not common, though it is sometimes seen.

Hemoglobin Content.—The diminution of this is the striking feature of chlorotic blood. Even when the red count is nearly normal, the hemoglobin-content is usually low. The percentage, however, never reaches the extremely low grades met with in the Addison-Biermer type or in the aplastic type of anemia. Values below 20 per cent (Sahli) are rare in chlorosis.

Color-index.—The low color-index is the most typical phenomenon in the blood of chlorosis. It may be very low, often as low as 0.5; in other words, each corpuscle may, on the average, contain only half its normal amount of hemoglobin.

White Blood-cells.—There are no marked alterations, either in the total count or in the differential formula, a helpful diagnostic point. When alterations are met with in chlorosis, they represent complications.

Blood Platelets.—These are often increased, in marked contrast with the condition in the Addison-Biermer type of anemia (Muir).

Other Blood-findings.—The total amount of blood is increased, as has been shown both by the infusion method and the CO method. Both the water of the blood and the protein of the blood are considerably increased in amount. There is a true polyplasmia. The coagulation time is normal, or shortened.

Prognosis.—Most patients do well if given plenty of iron, good food, fresh air, and rest. A few cases, however, have proved very rebellious to treatment, and have been subject to frequent recurrences. Some girls have an attack every year, over a long period. Once pregnant, the recurrences usually cease. Von Noorden has described a chronic form of chlorosis, dating from early childhood, in feeble girls, some of the cases remaining anemic throughout life, despite marriage. It may be that these are not true cases of chlorosis, but are instances of chronic hypoplasia of the hematopoietic organs (Naegeli).

Diagnosis.—There should be no difficulty, if the age of the patient, the sex, the blood findings, and the other symptoms described, be carefully considered.

Differential Diagnosis.—The disease must be differentiated (1) from *incipient pulmonary tuberculosis* (greater erythropenia, color-index not

so low, pulmonary signs, x-rays, tuberculin reaction); (2) from *Graves's disease* (cardinal symptoms, blood findings); (3) owing to the amenorrhea, from *beginning pregnancy* (blood findings, pelvic examination, Abderhalden reaction); (4) from *neurasthenic and hysterical states* (blood findings, exact psychic and neurological examination); and (5) from *other anemias* (blood findings, anamnesis, general physical examination).

(*b*) *Anemias Accompanying Tumors, Sclerosis, or Other Lesions of the Bone-marrow*

(*The Myelopathic Anemias*)

Under this heading, Morawitz has grouped the anemias that develop when the normal bone-marrow is largely replaced by tumor growths, by osteosclerosis, or by leukemic or pseudoleukemic proliferations. In all these conditions, the erythropoietic tissue is more or less suppressed. Anemia develops, and though extramedullary foci of erythropoiesis may develop in other organs like the spleen and liver, they are insufficient to supply the normal number of red corpuscles. Along with these processes, certain parts of the erythropoietic or leukopoietic marrow may be temporarily stimulated. This accounts for the appearance of nucleated red corpuscles, of neutrophilic leukocytes, and of myelocytes, in the blood in some of these conditions.

(*c*) *Anemias Accompanying Hypoplastic States of the Bone-marrow*

Such hypoplastic states include (1) those occurring in states of inanition and cachexia, due to chronic infections, or to malignant growths somewhere in the body, and (2) those of unknown origin.

i. Anemias Accompanying a Hypoplasia of the Bone-marrow Due to States of Inanition or Cachexia

Here belong the anemic states accompanying chronic disease such as (1) tuberculosis, (2) syphilis, (3) malignant neoplasms (carcinoma, sarcoma), (4) nephritis, and (5) other states of prolonged malnutrition. These anemias are often, accordingly, "secondary" anemias.

Blood Findings.—Red Blood-corpuscles.—Sometimes the pallor is due not to a diminution of the red count or of the hemoglobin in the volume unit, but to a diminution of the total quantity of blood—a true oligemia. But in the majority of cases there is also diminution in the red count per c.mm. and in the hemoglobin-content. In the fresh blood slide, there is usually no very marked anisocytosis or poikilocytosis, except in the severer forms. Nucleated red corpuscles, if present at all, occur in small numbers only, and are then almost always of the normoblastic type. Megaloblasts and macrocytes are absent, and there is no marked basophilic granulation of the red cells.

Hemoglobin Content.—This is reduced, usually in somewhat greater proportion than the number of red cells.

Color-index.—Usually below 1, though it may be nearly normal.

White Blood-corpuscles.—There is often a moderate leukocytosis, especially in the anemias accompanying neoplasms, a finding distinguishing this form of anemia both from the Addison-Biermer type and, more especially, from the aplas-

tic type. In the differential count, the leukocytosis is nearly always found to be of the neutrophilic type. Myelocytes are not present in the blood, as a rule; they occur if there are metastases of tumors in the bone-marrow.

It would seem that the hypoplasia of the bone-marrow in such cases affects chiefly the erythropoetic tissue, rather than the leukopoietic tissue.

Platelets.—There may be no marked alteration in the number of blood platelets. In some cases, they are diminished, and the coagulation time of the blood is delayed.

ii. Anemia Due to Hypoplasia of the Bone-marrow of Unknown Origin (Aplastic Anemia of Ehrlich; Aregeneratory Anemia of Pappenheim)

Definition.—The so-called aplastic anemia is a well-marked type of severe anemia, due to decreased blood formation from hypoplasia of the erythropoietic tissue of the bone-marrow.

Etiology and Pathology.—The cause is entirely unknown. At autopsy, a hypoplasia of the bone-marrow is obvious. The yellow marrow of the long bones is not changed into red marrow, and the bones that normally contain red marrow are found to be impoverished in nucleated red cells, the tissue of the marrow being made up chiefly of myeloblasts. There is a real atrophy of the marrow.

Symptoms.—An anemia of high grade develops, which might, on superficial examination, be thought to be of the Addison-Biermer type, but the lemon-yellow tint of the skin is lacking, and the urine is pale. There is a marked tendency to hemorrhagic diathesis.

Blood Findings.—Red Blood-corpuscles.—The findings differ from those of chronic hemolytic anemia in that, despite the great diminution in the number of red blood-corpuscles, there are no signs of accelerated erythropoiesis. The blood contains neither normoblasts nor megaloblasts, and there is no anisocytosis.

Hemoglobin Content.—This is reduced, usually *pari passu* with the number of red cells.

Color-index.—This is, accordingly, about normal.

White Blood-corpuscles.—The total count is markedly diminished. There is an outspoken leukopenia, depending upon a reduction in the number of white cells of myeloid origin, whereas the cells of lymphadenoid origin are not affected. There is, accordingly, a relative lymphocytosis, in this respect resembling the Addison-Biermer type.

Blood Platelets.—These are markedly diminished in number. The coagulation time is prolonged.

Diagnosis.—The high grade of anemia, in the absence of regeneration forms in the blood, with pale urine, rules out a chronic hemolytic anemia, and proves that we are dealing with an anemia due to deficient blood formation. The leukopenia, with relative lymphocytosis, distinguishes this aplastic anemia from the secondary anemias in cachectic states described above.

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B. Diseases in which the Number of Red Blood-corpuscles in the Volume Unit Are Increased (Polycythemia rubra)

We now come to a consideration of a group of conditions in which there is a more or less permanent increase in the red blood-corpuscles in the volume unit. These states are divisible into two great groups: (1) those in which the increase of the red corpuscles is symptomatic, accompanying other pathological states—the so-called *erythrocytoses;* and (2) those in which the increase of the red blood-corpuscles seems to be an independent disease of unknown etiology, associated with a hyperplasia of the erythropoietic tissue of the bone-marrow (the *erythremias*).

It will be noticed that the terminology here follows that of the analogous conditions in which the white cells are affected; namely, the leukocytoses and the leukemias.

1. The Erythrocytoses

Definition.—(See above.)

Classification.—Two main groups of erythrocytoses have been distinguished: (1) those accompanying chronic dyspneic states; and (2) those accompanying sojourn at high altitudes.

Etiology.—The actual cause of erythrocytosis is not known. In some of the cases, it seems to depend upon stimulation of the bone-marrow by lack of oxygen, but experimental work (Morawitz and Siebeck, Fitzgerald) indicates that, while this explanation may suffice for some of the erythrocytoses, it will not for all. The condition requires further study.

The Erythrocytoses in Chronic Dyspnea.—Among the conditions that give rise to chronic dyspneic states and that are accompanied by erythrocytoses may be mentioned (1) congenital heart disease, especially the morbus ceruleus due to pulmonary stenosis, (2) myocardial insufficiency in acquired heart disease, especially mitral disease, (3) stenosis of the respiratory passages (laryngeal stenosis, tracheal stenosis).

In congenital heart disease, the red count may reach 9½ millions. Certain individual factors must be considered, since not every case of congenital heart disease with cyanosis shows hyperglobulia. At autopsy, in the cases that manifest it, hyperplasia of the red marrow has been found.

In the myocardial insufficiency of acquired cardiac disease, erythrocytosis is not constant, and, when present, is of lower grade than in congenital heart disease. The number of red corpuscles rarely exceeds seven millions. In how far concentration of the blood, and in how far in-

creased formation of blood, are responsible for hyperglobulia is not known. When compensation is improved, hyperglobulia often diminishes; this speaks in favor of an altered distribution of the red corpuscles, or of a concentration of the blood.

The erythrocytosis associated with stenosis of the upper air passages rarely reaches a high grade. In experimental animals, and in experiments on man with Kuhn's mask, a moderate hyperglobulia can be produced in a short time.

The erythrocytosis associated with the cyanosis of extreme emphysema should be studied more carefully.

Erythrocytosis on Sojourn at High Altitudes.—People living at an altitude, usually have a higher red-cell count than normal (5.5-7 millions). It has often been asserted that the number stands in fairly direct proportion to the altitude, but this is disputed.

We must distinguish between the increase in the red corpuscles that occurs immediately after going from a low level to an altitude (as in the rapid ascent of a mountain, in a balloon ascension, or in an air-ship trip), and that which occurs after longer sojourn in high places. In the former case, a new formation of red corpuscles cannot account for the increase, and there are no signs in the blood of accelerated erythropoiesis, such as nucleated reds or polychromasia. This form or erythrocytosis must be due to altered distribution of blood (Zuntz, A. Loewy), or to concentration of the blood (Grawitz), probably to the former.

On the other hand, the erythrocytosis following upon longer sojourn at high altitudes is probably due to increased erythropoiesis.

Experimental Erythrocytosis Following Injection of Epinephrin.—In a recent research Lamson, in Abel's laboratory, has found that polycythemia may be easily produced experimentally in animals in different ways, especially by the injection of epinephrin. He concludes that there is a mechanism for the regulation of the red-corpuscle content of the blood; that this regulatory mechanism is under nervous control, reacting to lack of oxygen as a stimulus; that the adrenal glands play a part in this mechanism; and that the liver is the organ that supplies the body with red cells to meet its acute demand.

2. The Erythremias

(Vaquez's Disease, Osler's Disease)

Definition.—By erythremia is meant a disease in which there is an increase in the total number of red blood-corpuscles, and in the total quantity of blood, without discoverable cause, usually associated with splenomegaly, and often with cyanosis and constipation. It was first described by Vaquez (1892), but became more generally known through the

researches of Osler (1903), who first put the disease on a firm clinical basis.

Etiology.—This is entirely unknown.

Symptoms.—The onset is insidious, usually in middle life, with headache, dizziness, pains in the region of the spleen and liver, cherry-red color of the face, ears, and mucous membranes.

The splenomegaly varies in degree, but is usually not excessive. The spleen is hard, and, if enlarged enough for the surface to be felt, is smooth. The liver is sometimes palpable. The blood pressure is not necessarily high, though in one group of cases, described by Geisboeck as "polycythemia hypertonica," there is arterial hypertension. It is surprising that the heart is not more involved, considering the increased viscosity of the blood, but, evidently, other circulatory mechanisms compensate, so that the work of the heart is not essentially increased. Constipation is often a marked feature.

Summary of the Blood Findings.—Red Blood-corpuscles.—The number is greatly increased, averaging between 7 and 10 millions. In one case, 13 millions were found (Koester). The number often varies markedly, in different periods, in the same person.

The fresh blood is thick and sticky, and of a darker color than normal. The stickiness is especially noticeable on making smears. Normoblasts are occasionally present, rarely megaloblasts. Polychromasic cells are common, and there is sometimes a little anisocytosis; these phenomena point, of course, to accelerated erythropoiesis.

Hemoglobin Content.—This is markedly increased, but not to so high a grade as the number of red corpuscles. The values vary between 120 and 150 (Sahli). In Koester's case, the hemoglobin was 240 per cent.

Color-index.—This is usually less than 1.

White Blood-corpuscles.—The total count is usually somewhat increased. A neutrophilic leukocytosis is occasionally seen, and a few myelocytes may be met with in the blood (Türk).

Platelets.—These are usually somewhat increased.

Other Blood-findings.—The total amount of blood is increased (Morawitz and Siebeck, Parks Weber, A. Loewy). The viscosity is greatly increased, owing to the polycythemia rubra. The blood serum may contain a normal amount of protein (Bence), or it may be protein-poor (Weintraud). The coagulation time may be shortened; sometimes it is normal.

Complications.—Some of these patients suffer from severe hemorrhages (epistaxis, enterorrhagia), even when the blood pressure is not high. Meningeal hemorrhage, or cerebral hemorrhage, sometimes occurs, and may be fatal. Thrombosis of the cerebral vessels and of the splenic vessels, with infarct production, is not uncommon.

Prognosis.—The course of the disease varies much in different cases. Mild cases may suffer but little inconvenience, and may live a long time. In the severer cases, the outlook is grave, but there may be gratifying remissions, even in these. McLester has been able in a case he has studied to keep the red count down by administering benzol.

Pathological Anatomy.—The findings at autopsy show a hyperplasia of the erythropoietic tissue (Weber and Watson, Lommel). Red marrow is found in many places where yellow marrow is normally present. There may also be extramedullary erythropoietic foci, especially in the spleen (Hirschfeld). The enlargement of the spleen is, however, most often due to infarcts, hemorrhages, cysts, or simple hyperemia. The vessels at autopsy are everywhere greatly distended with blood.

The disease is undoubtedly due to increased production of red cells rather than to abnormal length of life of the corpuscles. The urobilin-output is high. The oxygen-capacity of the hemoglobin is normal (Butterfield). The total gas-metabolism is increased (Senator) as a rule, though in some cases there is no change (Grafe).

We have no clew to the stimuli that cause the pathologically-increased erythrocytosis.

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C. The Leukemias

Definition.—By leukemia is meant a condition in which there is extensive proliferation of the leukopoietic tissues of the body, either lymphadenoid or myeloid, with the appearance in the blood of white blood cells not normally present. There is, usually, at the same time, an increased number of the normal white cells, but not always.

Historical.—Leukemic states were first recognized, at autopsy, by Virchow (1845), and soon after the disease was recognized during life by Vogel.

Our knowledge of leukemia has, however, undergone remarkable development since then. We have learned, in the first place, to distinguish between the leukocytoses and the leukemias, not on the ground of the total white count, for there are sometimes leukocytoses with more than 100,000 white cells per c.mm., and there are often leukemias with less than 50,000 leukocytes per c.mm., though as a general rule the total count is much greater in leukemia than in leukocytosis. An important step forward was also made when it was recognized that qualitative deviations in the white cells are more important for differentiation than quantitative changes in the total count. This step was taken by Ehrlich, and followed the introduction, by him, of differential counting of electively-stained smears. It was soon found that, in some cases of leukemia, cells of lymphadenoid origin predominate, and that, in other cases of leukemia, cells of myeloid origin predominate. For a time it was thought that the presence of myelocytes in the blood was sure evidence of the existence of a leukemia, but later on the non-leukemic myelocytoses (bone-marrow carcinosis, anemia pseudoleukemica infantum) came to be recognized. Finally, clinical and autoptic studies have demonstrated that proliferations of either the lymphadenoid or the myeloid tissue, wholly similar to those that occur in the leukemias, may take place without the appearance of immature cells in the blood (aleukemic lymphadenoses and myeloses, *q. v.*).

Though in the majority of instances a diagnosis can be made by a differential count of the white blood-cells alone, it must be emphasized that, in some cases,

the blood-picture by itself is insufficient for diagnosis. As in most clinical studies, we should never depend upon any one method of examination, no matter how helpful this may be, but should study the patient as a whole, by all available diagnostic methods, before drawing our final conclusions.

On acount of the great enlargement of the spleen in some forms of leukemia, it was by some thought that leukemia is splenogenous in origin; but we know now that this is not true, and that the leukemias are divisible into two great groups: (1) those of lymphadenoid origin, and (2) those of myeloid origin.

Leukemia is not, however, a disease of an organ, but in all cases represents a pathological productivity of tissues, widespread throughout the body—in the one group of cases, the lymphadenoid tissue all over the body, in the other group of cases, the myeloid tissue of the marrow of the various bones of the skeleton. In order to tell which of these tissues is undergoing proliferation, we study especially the forms of the abnormal white cells that appear in the blood; in other words, the blood-change is not primary in the leukemias, but is, on the contrary, a secondary phenomenon. The primary condition is the pathological stimulation to proliferation of a definite kind of leukopoietic tissue, and this hyperplasia of the lymphadenoid tissue, on the one hand, or of the myeloid tissue, on the other, may precede for some time the appearance of the leukemic blood-picture; in other words, the lymphadenoid leukemias may be preceded by an aleukemic lymphadenosis, and the myeloid leukemias may be preceded for a time by an aleukemic myelosis.

Aside from the characteristic morphological differences already described between white corpuscles of lymphadenoid origin and white corpuscles of myeloid origin, it is the behavior of the blood in pathological states, such as the leukemias, that has led me to adopt the dualistic doctrine of the origin of the white corpuscles, and in this I find myself in agreement with the majority of present-day clinical hematologists.

Frequency and Distribution.—Leukemia is a relatively rare disease. That we see it more commonly now than formerly, is probably no indication of a greater frequency, but rather due to the fact that blood examinations are more common, that the disease is better known, and that it is now more often recognized. Statistics indicate that, in hospital practice, there are only one or two leukemic patients per thousand admissions.

The disease is commonest in middle life, but may occur at any age. Both acute and chronic forms are recognized. In children and young adults, the disease is most often acute. Men are somewhat more frequently attacked than women.

Leukemia is met with in human beings in all parts of the world. It is also seen in animals; Nocard has described it in horses, cattle and dogs; Ellermann and Bang, in chickens. Thus far, it has not been observed in guinea-pigs, nor in rabbits. Myeloid forms of leukemia appear to be somewhat more common than lymphadenoid forms.

For a full description of leukemia in fowls, see the article by Schmeisser.

Etiology.—This is entirely unknown. There is some evidence that favors the idea that it is of infectious origin. I have, personally, been struck with the num-

ber of instances of myeloid leukemia in which the patients have described to me an earlier, severe, pyogenic infection. In one case of lymphatic leukemia, a patient, whom I saw with Dr. T. R. Brown, had been bitten a few months before by an insect in Switzerland, the insect bite being followed by a severe phlegmon. In a case of myeloid leukemia, shown me by Dr. H. A. Macallum, of London, Ont., the condition developed some time after a most extensive suppurative process.

Various supposed parasites (amebae of Loewit; azure-staining, rodlike inclusions of Pappenheim) have been described in the white cells, but there is, as yet, no evidence that these are etiological agents.

We must hope that work on the experimental leukemias of animals may before long throw light upon the etiology. Chicken leukemia can be transferred from bird to bird (Ellermann and Bang, Schmeisser), either by injection of the whole blood, or of the cell-free serum. Attempts to transfer leukemia from dog to dog have thus far failed (Weil and Clerc).

Forms of Leukemia.—It is very easy to distinguish chronic myeloid leukemia from chronic lymphadenoid leukemia by the blood picture. It may be extremely difficult to distinguish acute lymphadenoid leukemia from acute myeloid leukemia by the blood picture, or indeed by any other method during life, though the separation of the two at autopsy is relatively easy. A very skilled hematologist may, it is true, distinguish the cells of acute myeloid leukemia from those of acute lymphadenoid leukemia, but even he may have to resort to special methods, very delicate in their nature, and it is too much to ask the general practitioner to make the distinction. As yet, the differential diagnosis between these two forms of acute leukemia is of no practical importance, for in both types, the disease runs a rapid and fatal course, and neither type is amenable to any form of therapy. For didactic reasons, however, I shall describe the myeloid leukemias, both acute and chronic, entirely separate from the lymphadenoid leukemias, chronic and acute. It is highly important that this fundamental division be recognized by students and practitioners.

1. The Myeloid Leukemias

(*The Leukemic Myeloses*)

Chronic myeloid leukemia is the most common form of leukemia. It is much more common than acute myeloid leukemia.

(*a*) *Chronic Myeloid Leukemia*

(*Chronic Leukemic Myelosis*)

Symptoms.—The onset is insidious, and the disease has usually progressed far before the patient consults a physician. Usually, it is the enlargement of the spleen, or a progressively increasing weakness or pallor, that brings the patient to consultation.

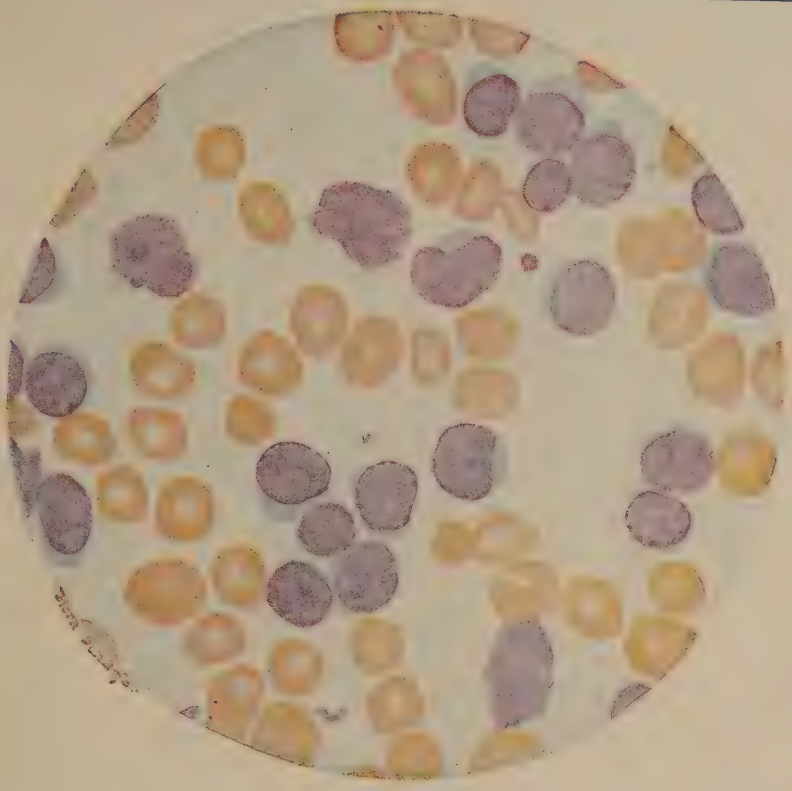

Fig. 1.—Lymphatic Leukemia. Wilson Stain. × 800. (Original Drawing.)

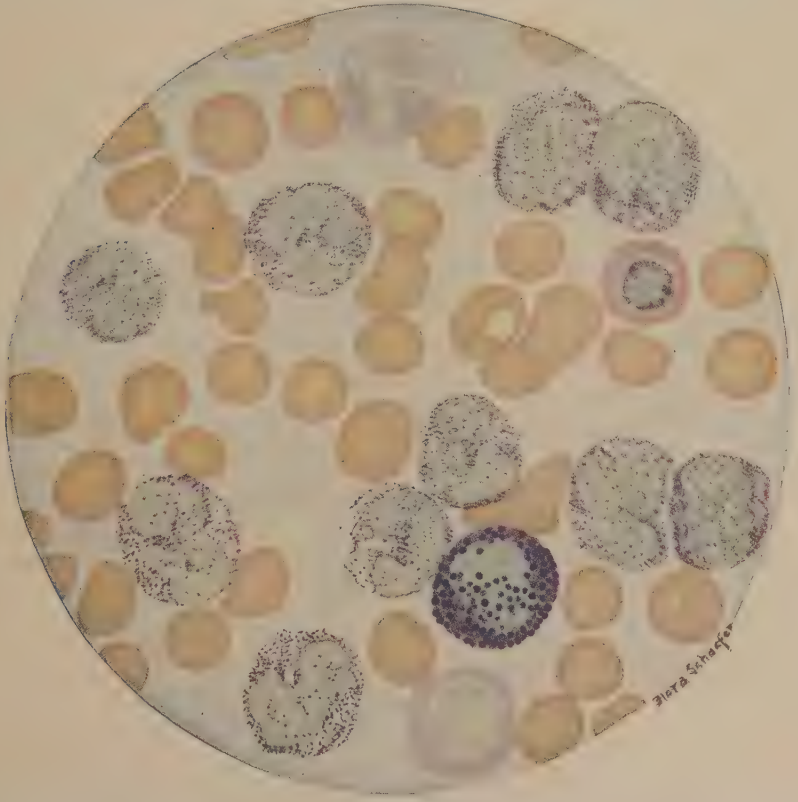

Fig. 2.—Myelogenous Leukemia Showing Neutrophilic Myelocytes, Eosinophilic Myelocyte, Mast Cell, Nucleated Red Cell, and a Myeloblast. Ehrlich Stain. × 800. (Original Drawing.)

On close analysis, various subjective symptoms may have been noticed (heavy feeling and pains in the left side of the abdomen, digestive disturbances, weakness, palpitation, dyspnea, emaciation). Sometimes hemorrhages occur early (epistaxis, retinal hemorrhage, labyrinthine hemorrhage).

On physical examination, there is pallor, usually emaciation, sometimes petechiae and other signs of hemorrhagic diathesis, such as spongy gums. The most important sign is enlargement of the spleen, due to the development in it of extramedullary leukopoietic foci of myeloid type. On palpating the abdomen, the physician may be surprised to find an enormous organ, and, strange to say, in many cases, the patient has not noticed it. It is nearly always some fingers' breadth below the left costal margin, and in some cases fills up the whole left side of the abdomen; I have even seen it extend over into the right abdomen far beyond the umbilicus. It may not be tender, though, if perisplenitis has occurred, tenderness may be elicitable, and sometimes friction fremitus. The surface is smooth. The notch in the spleen can usually be felt. The consistence is firm.

The lymph glands may be somewhat enlarged owing to extramedullary leukopoietic foci of myeloid nature. The liver is also usually enlarged, due to the presence in it of leukopoietic foci. The bones, especially the sternum and ribs, may be tender on percussion.

Many patients have irregular fever; some have night sweats, signs that, erroneously, sometimes lead to a diagnosis of pulmonary tuberculosis.

There are usually digestive disturbances (anorexia, diarrhea, constipation) variable in degree.

The urine often shows deposits of urates, and the uric-acid content of the urine and of the blood is high, owing to disintegration of leukocytic nuclei. An actual attack of gout may be precipitated by x-ray treatment. Aside from the disturbances of purin metabolism due to disintegrating nuclei, no marked metabolic disturbances have been made out. Examinations of gas metabolism yield as a rule normal values.

In the nervous system, aside from visual, cochlear and vestibular disturbances due to hemorrhages in the retina or in the labyrinth, there may be paralyses, due to cerebral hemorrhage, or sometimes symptoms referable to lesions of the posterior and lateral funiculi, as in all cases of severe anemia.

Summary of the Blood Findings in Chronic Myeloid Leukemia.—Red Blood-corpuscles.—The number varies much. It may be normal at the beginning, but later on anemia develops. It is not uncommon to find signs of accelerated erythropoiesis, even before anemia appears (normoblasts, polychromasia, basophilic granulation of red corpuscles). Megaloblasts do not occur unless the anemia becomes marked.

Hemoglobin Content.—This conforms closely to the decrease in number of red corpuscles, but is a little more marked.

Color-index.—This is, accordingly, somewhat lower than normal when anemia has developed.

White Blood-corpuscles.—It is, to some extent, the quantitative, but, more especially, the qualitative, change in the white blood-cells that is so striking in the blood in myeloid leukemia. The total count is usually very high, averaging between 100,000 and 200,000, sometimes reaching 500,000 per c. mm., rarely more. In some cases, there are periods when the total white count is only slightly increased, but even then the differential count permits of a positive diagnosis as a rule.

The deviation from the usual differential formula in stained smears is characteristic; in the majority of cases, the blood picture is dominated by the presence of a large number of n-myelocytes though there is also a great increase in the polymorphonuclear eosinophils and in the polymorphonuclear basophils; usually, too, e-myelocytes and b-myelocytes are also present. The greatest increase of all is usually in the polymorphonuclear neutrophils. Not only is their absolute number enormously increased, but they often maintain their normal percentage-relationship in the blood, averaging 60-70 per cent of all the white elements. Not infrequently, a number of transition forms between n-myelocytes and polymorphonuclear neutrophils are present; these are the so-called n-metamyelocytes.

There is usually both a relative and an absolute increase in the polymorphonuclear eosinophils and the polymorphonuclear basophils; together, they may make up 10 per cent of all the white cells. In rare cases, the polymorphonuclear basophils are present in excessive numbers, so that they dominate the blood picture (so-called "mast-cell leukemia").

The percentage of n-myelocytes present may be very large, but it is so variable that it is scarcely worth while to give figures. These cells vary greatly in size. Occasionally karyokinetic figures are visible in them. The granules of the n-myelocytes often stain unevenly, immature granules with basophilic tendency being interspersed among the typical neutrophil granules. In the e-myelocytes, immature granules with basophilic tendency can also be seen among the red e-granules.

Besides the myelocytes, myeloblasts are also present, in most cases, in greater or less numbers, and they may be accompanied by transition forms between them and the myelocytes; these transition forms are the so-called pro-myelocytes. In exacerbations of the disease, there is usually a great increase in the myeloblasts in the blood. This is particularly true of the exacerbations following the favorable remissions due to x-ray treatment or to benzol treatment.

The small mononuclears or lymphocytes are present in about their normal absolute numbers, but, on account of the great increase in the

cells of myeloid origin, the relative number of small mononuclears is greatly diminished. The large mononuclear and transitional forms are, as a rule, not increased. This is rather surprising if, as many of us believe, they are of myeloid origin. It would seem that, even in the myeloid proliferation, the stimulus producing it exerts an elective influence.

Blood Platelets.—The number is usually increased.

Other Blood-findings.—The total amount of blood appears to be somewhat increased, though exact studies are not available. The coagulation time is lengthened, notwithstanding the fact that the blood platelets are increased in number. The fibrinogen is diminished.

Atypical Blood-pictures in Myeloid Leukemia.—The summary given above applies to the average case, but remarkable deviations from this typical picture are not infrequently met with. The deviations from the type may follow any one of three directions: (1) the total white count may be nearly normal, especially in early stages or after treatment (x-ray, benzol, arsenic), or after some intercurrent infectious disease (typhoid, sepsis, tuberculin injections); (2) the increase in the polymorphonuclear eosinophils and in the polymorphonuclear basophils may be absent; (3) the white cells may consist, to a very large extent, of myeloblasts, especially in acute exacerbations.

Duration and Termination of the Disease.—The disease is incurable, though long remissions may occur, especially after certain therapeutic efforts. The average duration is 2-4 years, though I know of cases living ten years after a positive diagnosis had been made. As a rule, the disease advances more or less steadily, the splenomegaly becomes ever more marked, the cachexia increases, the anemia increases, and death ensues from general weakness or more often from terminal infection or hemorrhage. The remissions are at times very gratifying, but unfortunately the hopes engendered are not long supported. Too often, the exacerbation that follows a remission leads to a clinical picture of severer type than any previously experienced; the chronic leukemia may take on the features of an acute leukemic process (predominance of myeloblasts).

At autopsy, the proliferation of myeloid leukopoietic tissue is the characteristic feature. It involves not only the normal red marrow, but also the marrow of the long bones, the spleen, the liver, certain of the lymph glands, the kidneys, and sometimes the serous membranes and the skin.

(*b*) *Acute Myeloid Leukemia*
(*Acute Leukemic Myelosis*)

This, though a rare disease, is commoner than has heretofore been suspected. Many of the cases formerly described as acute lymphatic leukemia are now known to have been acute myeloid leukemia, in which

the white cells consist almost entirely of Naegeli's myeloblasts. For scientific accuracy, in cases of acute leukemia one should try to distinguish between myeloblasts and lymphoblasts. If n-myelocytes and promyelocytes are present, the differentiation is helped. Otherwise, one has to depend upon the demonstration of the indophenyl-blue synthesis in the myeloblasts (never present in lymphoblasts), or upon other subtle hematological staining-reactions (*q. v.*)

Acute myeloid leukemia runs the course of an acute malignant infectious disease, with high fever, hemorrhagic diathesis and rapidly developing anemia. Normoblasts often appear in the blood.

At autopsy, the findings resemble those of chronic myeloid leukemia and include typical perivascular proliferations of myeloid leukopoietic tissue, both intramedullary and extramedullary (spleen, liver, etc.). In these proliferations, myeloblasts may predominate, but in their staining-reactions and in their distribution the cells of these myeloblastic proliferations differ from the cells of the proliferations of lymphadenoid tissue met with in acute lymphadenoid leukemia.

2. The Lymphadenoid Leukemias

(*Leukemic Lymphadenoses, Lymphatic Leukemias*)

Here, too, we distinguish a chronic form from an acute form. It is interesting that most chronic leukemias are myeloid and not lymphadenoid. Most acute leukemias have hitherto been supposed to be lymphadenoid, but recently it has appeared more probable that the acute leukemias also are more often myeloid than lymphadenoid in nature.

(*a*) *Chronic Lymphadenoid Leukemia*

(*Chronic Leukemic Lymphadenosis, Chronic Lymphatic Leukemia*)

Symptoms.—The onset is insidious. The patient begins to grow pale, to feel weak, and perhaps to suffer from dyspnea and palpitation. He may early notice a little enlargement of the neck due to swelling of the cervical lymphglands.

On examination, one finds, on palpation of the regional lymphglands in various parts of the body, a general lymphgland enlargement. The cervical glands are usually the largest, but the axillary and inguinal lymphglands are also enlarged. The enlargement is, as a rule, not great; the glands may be of the size of beans, rarely larger than hickory-nuts. They are fairly firm, a little sensitive on pressure, and can be moved about freely in the subcutaneous tissue, never being adherent to the skin. The tonsils are also often enlarged. Occasionally, there are lymphoid nodules in the skin itself, not unlike what is seen in mycosis fungoides.

The spleen is palpable, sometimes quite large, but never attaining to

anything like the size met with in chronic myeloid leukemia. It is firm and smooth. The enlargement rarely permits one to feel the notch. The liver is usually somewhat enlarged and firm.

The endogenous-uric-acid content of the blood and of the urine is increased. Occasionally, there is albuminuria and cylindruria. Bence-Jones body may be present (Askanazy), but this does not distinguish the process from myeloid leukemia, as Boggs and Guthrie have found Bence-Jones body in the urine of that disease.

In a typical case, the palpable lymphglands may not be enlarged, even when the blood picture is conclusive. We must assume that, in such cases, the hyperplasia affects especially the internal lymphglands (bronchial, mediastinal, retroperitoneal, mesenteric).

Irregular fever of low grade may accompany the process.

Summary of Blood Findings in Chronic Lymphadenoid Leukemia.—Red Blood-corpuscles.—The number may be normal, though, as a rule, there is some anemia, and occasionally it is of high grade. Nucleated reds (normoblasts) are far less common than in chronic myeloid leukemia, but if the anemia reach a high grade, normoblasts appear as well as polychromasic forms.

Hemoglobin Content.—This follows the total red count closely, but the hemoglobin is usually a little more reduced.

Color-index.—This is, accordingly, either normal, or a little lower than normal.

White Blood-corpuscles.—The total count is high, averaging between 100,000 and 500,000. The qualitative changes in the differential count are remarkable. The small mononuclear elements, or lymphocytes, dominate the blood picture, the increase in the white cells consisting entirely of these cells. As a result, the white corpuscles of myeloid origin (polymorphonuclears, large mononuclears and transitionals) make up only a very small percentage of the total count, though their absolute numbers may be normal, or only slightly diminished.

In this chronic disease, the lymphocytes present are chiefly of the small variety, though these may differ from normal small lymphocytes in that the azure granulation is present in a smaller proportion of the cells than normal, or it may be absent altogether (Naegeli). In addition to the small lymphocytes, larger forms frequently appear, either ordinary large lymphocytes (*q. v.*) or Rieder cells (*q. v.*). Sometimes plasma cells are also present.

In rare cases, the majority of the white cells may be large lymphocytes, and these may contain azure granules (Naegeli); Sternberg regards these cases as sarcomatoses, but his view has not yet been generally accepted.

Morawitz emphasizes the "uniformity" of the blood picture in chronic lymphadenoid leukemia, as contrasted with the "variety" of the blood picture in chronic myeloid leukemia, and with this all experienced clinical observers will agree; in

the former instance, the white cells of the smear are almost entirely small mononuclear elements; in the latter instance, the smear is "variegated," being crowded with a great variety of white cells (polymorphonuclears, mononuclears, all kinds of granulations).

Blood Platelets.—These may be diminished in number, and the coagulation time is lengthened.

Duration of the Disease.—As in chronic myeloid leukemia, though there is a general tendency to progression, the course of the disease is usually marked by remissions and exacerbations. The prognosis is about the same as in chronic myeloid leukemia. Patients may die within a few months, or they may live longer than a decade. As far as we know, complete recovery does not occur. The lymphadenoid hyperplasia is more or less amenable to therapeutic measures (x-rays, benzol, radium), but the results are not so striking, as a rule, as in chronic myeloid leukemia. Death usually occurs from some intercurrent infection (sepsis), from the hemorrhagic diathesis, or from a progressive cachexia.

Autopsy Findings.—There is generalized hyperplasia of the lymphadenoid tissue throughout the body (lymph glands, spleen, bone-marrow, Peyer's patches and solitary follicles of the intestine, tonsils, parenchymatous organs). In the bone-marrow, the myeloid tissue is more or less suppressed by accumulations of foci of lymphoid cells (lymphadenoid tissue).

(*b*) *Acute Lymphadenoid Leukemia*

(*Acute Leukemic Lymphadenosis, Acute Lymphatic Leukemia*)

This is a rare disease, though consultants are apt to see it, owing to its peculiar manifestations. I have seen a good many cases of it during the past ten years.

The onset is sudden, like that of an acute infectious disease, and without apparent cause. It is commonest in children and in young people, though it may occur at any age. In my experience, it is invariably fatal, usually within about two months after onset, never lasting over a third of a year. Cases lasting longer than this come under the head of chronic lymphadenoid leukemia. All the cases of lymphadenoid leukemia that I have seen in children have been of the acute type.

Baetjer and Miller have collected a series of cases in which, though the blood picture seemed to be that of lymphadenoid leukemia, the patients recovered. Whether these were instances of true leukemia or of non-leukemic lymphocytosis accompanying infections is still in doubt.

Symptoms.—The disease is ushered in with rapidly rising temperature, headache, pains in the limbs, sometimes with vomiting, often with chill. The patients may complain of symptoms referable to the mouth or throat, such as difficulty in swallowing, or pain on mastication. The

gums quickly become spongy and begin to bleed, and soon a general hemorrhagic diathesis develops.

Every physician should know that an acute febrile disease in a young person, associated with severe stomatitis, with hemorrhages from the gums, and with the development of a general hemorrhagic diathesis, is very suggestive of acute leukemia, and that the blood should be immediately examined.

The tonsils are often involved, becoming swollen, red, and sometimes covered with a whitish, foul exudate. Though the cervical lymphglands may be enlarged, there is no lymphgland enlargement as a rule at the beginning. Even the spleen may not be palpable at first. The urine contains albumin and casts, and usually, an excess of uric acid. As the disease progresses, a general lymphgland enlargement of moderate grade may appear.

Summary of the Blood Findings.—During the first few days the blood may not show any very striking changes, but usually by the end of a week, at the latest, the outspoken signs of acute leukemia appear in the blood.

Red Blood-corpuscles.—These are present in normal numbers at first, but as the disease progresses, the red-cell count diminishes, and a more or less high grade of anemia may develop, in which event, nucleated red cells may appear in the blood, though they are less common than in acute myeloid leukemia.

Hemoglobin Content.—This runs nearly parallel to the red-cell count, though, when a high grade of anemia develops, the hemoglobin is often more diminished than the red cells.

Color-index.—This is normal, or nearly normal, at the beginning, but as anemia develops, it becomes less than 1.

White Blood-corpuscles.—At the very beginning, the total white count may be normal, or only a trifle higher than normal (aleukemic stage), but in a few days the total count quickly runs up to 100,000 or 200,000 per c. mm., in some cases reaching 500,000 per c. mm. When the total count has become increased, the differential count also shows a remarkable transformation. Nearly all the white corpuscles are mononuclear cells, often as many as 95 per cent of the total count consisting of lymphocytes, among them, many large lymphocytes and Rieder cells.

When one sees that 90-95 per cent of the white cells are of the lymphocytic type, and the onset has been acute, with stomatitis, fever, and the rapid development of a hemorrhagic tendency, one can be sure that he is dealing with an acute leukemia and that it will soon terminate fatally

As has been pointed out, only a skilled hematologist can say positively, in some cases of acute leukemia, whether the cells are of lymphadenoid origin or of myeloid origin. There will even be difference of opinion among men who have worked

much with differential stains. If the criteria, established by Naegeli, for lymphadenoid cells on the one hand, and for myeloblasts on the other, be accepted, and the blood be studied by methods that reveal the differences mentioned, a definite conclusion can, as a rule, be arrived at. For practical purposes, however, this is not of great significance, since it is the diagnosis of acute leukemia that is of importance, at present, rather than a distinction between the lymphadenoid and the myeloid types; in both cases, death invariably results within a short time.

It must not be forgotten that a few myelocytes may occur in the blood in acute lymphadenoid leukemia; should such be found, they must be looked upon as signs of an "irritation myelocytosis," dependent upon lymphadenoid proliferation in the bone-marrow (Morawitz).

Blood Platelets.—These are usually diminished in acute lymphadenoid leukemia.

Etiology.—The cause of acute lymphadenoid leukemia is entirely unknown.

In many instances streptococci are found in the blood, especially toward the end of the disease, probably a secondary not a primary infection, the resistance being lowered by the absence of white corpuscles of myeloid origin. Some authors, however, believe that acute leukemia may itself be the sign of an acute septic infection (Sternberg, Ziegler, Jochmann).

Pathology.—At autopsy, the histological lesions are very much like those in chronic lymphadenoid leukemia, though the proliferation of lymphatic tissue is not quite so extensive, and there may be more large lymphocytes and Rieder forms than in the chronic disease. Isolated masses of lymphadenoid tissue, suggesting tumor formation, are sometimes seen, especially in the thymus and in the mediastinal glands, and the differential diagnosis from lymphosarcoma may then be difficult.

Differential Diagnosis.—(1) From *primary septic disease;* (2) from the *simpler forms of stomatitis and tonsillitis;* (3) from *other diseases associated with hemorrhagic diathesis.*

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D. States More or Less Resembling Leukemia (The So-called Pseudoleukemias and Leukemoid Diseases)

We must now consider a group of diseases concerning which a vast deal of confusion prevails in medical writings, for the reason that, for a long time, a group of wholly different diseases resembling one another closely and in turn as a whole resembling to some extent the conditions in leukemia were not distinguished from one another, but were grouped together as pseudoleukemias (Cohnheim). Gradually medical men have learned how to separate from this group, one after another, certain definite disease-entities. If the term pseudoleukemia be used at all now it should

be used for the whole group, and with the clear consciousness that the states subsumed under this heading may be pathogenetically wholly unrelated to one another, just as we use the term jaundice to designate a symptom in a number of wholly unrelated diseases. I am hopeful that, before long, we may discard the term pseudoleukemia altogether, and keep, in our medical terminology of the states now included under it, only the names that designate really different disease-entities. For historical reasons, however, and on account of the vogue of the term in medical writings generally, it seems necessary still to explain the sense in which the pseudoleukemias have been and are now understood. Among these pseudoleukemias and leukemoid states have been included the following: (1) aleukemic lymphadenosis; (2) aleukemic myelosis; (3) chronic infectious granulomatous processes involving the lymph glands, (a) Hodgkin's disease, (b) tuberculosis of the lymph glands, (c) syphilis of the lymph glands; (4) the leukemoid diseases, (a) lympho-sarcomatosis (Kundrat), (b) the chloromas, and (c) the myelomas (Kahler). After this introductory statement, these several diseases will now be separately described.

1. The So-called Pseudoleukemias

(*a*) *Aleukemic Lymphadenosis*

Definition.—A disease characterized by a diffuse, generalized hyperplasia of the lymphadenoid system all over the body (lymph glands, spleen, bone-marrow, tonsils, lymphatic tissue of mucous membranes and parenchymatous organs), histologically indistinguishable from the lymphadenoid hyperplasia met with in the lymphadenoid leukemias, but not associated with a leukemic blood-picture.

It will be seen that this disease is distinguishable from lymphatic leukemia only by the absence of an increase of the lymphocytes in the blood. Like lymphadenoid leukemia, it may occur either in a chronic or in an acute form. The close relationship of the two diseases is further emphasized by two facts: (1) a lymphadenoid leukemia may be preceded by a stage of aleukemic lymphadenosis, and (2) an aleukemic lymphadenosis may, after persisting for a long time, suddenly and without apparent reason, go over into a lymphadenoid leukemia. One cannot help but feel that the etiology of aleukemic lymphadenosis and of lymphadenoid leukemia must have something in common, but why it is that a leukemic blood-picture develops in some cases with the lymphadenoid proliferation, and not in others, we were utterly unable to explain. Obviously, some factor other than the main etiological factor causing the lymphadenoid proliferation must enter in to account for the development of a leukemic blood-picture.

Symptoms.—The symptoms in aleukemic lymphadenosis (chronic and acute) are the same as those of lymphadenoid leukemia (chronic and

acute), except for (1) the difference in the blood findings, and (2) a somewhat more favorable prognosis, or at any rate, a longer duration.

Diagnosis.—In the chronic forms the diagnosis can be made only through excision of an enlarged lymphgland and histological examination of the gland. This will sharply separate the disease from the various infectious granulomata, while the blood picture separates it from the leukemias. In the acute form of aleukemic lymphadenosis, the diagnosis can rarely be made during life, though it may be suspected. The true nature of the disease is revealed first by the autopsy findings.

(*b*) *Aleukemic Myeloses*

There are, apparently, rarer than aleukemic lymphadenosis, but recently single cases of so-called myeloid pseudoleukemia, or of aleukemic myelosis, have been described (Hirschfeld). This disease stands in precisely the same relation to the myeloid leukemias as does aleukemic lymphadenosis to the lymphadenoid leukemias. The fact that it is rarer may depend upon the more intimate relation of the myeloid leukopoietic tissue to the blood vessels, so that proliferations of this tissue are more often associated with a leukemic blood-picture than is the lymphadenoid proliferation.

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(*c*) *Chronic Infectious Granulomatous Processes Involving the Lymph Glands*

Knowledge of the infectious granulomata involving the lymph glands has made great progress, especially in American clinics, and the American bibliography is much clearer on this subject than the European. It is somewhat surprising that European observers seem still to be more or less confused with regard to this group of diseases. Recently, however, American work has become better known in the European clinics, and some of the European writers, notably Morawitz, Naegeli, and Pappenheim, discriminate clearly among the various diseases of the group.

In America, through the influence largely of Osler, the prevalence of Hodgkin's disease has become well recognized, and thanks to the researches

of Dorothy Reed, of Longcope, and of McCallum, the histological picture has been so sharply characterized that we now have no difficulty when the lymph glands are enlarged in diagnosing Hodgkin's disease, provided we are permitted simply to make a histological examination of a lymph gland removed *intra vitam*. Moreover, recently, the bacteriological studies of Bunting and Yates in this country, and of Negri and Mieremet abroad, have revealed the frequent presence of a definite diphtheroid bacillus in the glands in Hodgkin's disease, a discovery that has been quickly turned to therapeutic purposes by Billings and Rosenow in Chicago.

Bunting's ideas on the subject (1915) may be formulated as follows (personal communication):

Among lymphglandular enlargements, he finds a group subdivisible histologically into three types—

(1) An inflammatory type, *e. g.*, Hodgkin's disease.

(2) A large-celled proliferation-type.

(3) A small-celled proliferation-type.

Each of these may, or may not, be associated with extraglandular tumors.

Hematologically, in these cases he finds:

(1) The white-blood-cell picture that he has described in the early stage of Hodgkin's disease, or

(2) A leukemic blood-picture with the predominant cell of the same type as that seen in the sections of the glands.

On making bacteriological cultures, Bunting finds that a diphtheroid organism may be cultivated apparently readily from all three types. Though he has not had a large number of cases, he has had positive cultures (1) from twelve cases of Hodgkin's disease; (2) from four of the large-celled proliferation-type (aleukemia); and (3) from two of the small-celled proliferation-type, one of them with, the other without, a leukemic blood-picture. In only one of the Hodgkin's cases were the cultural results negative.

Clinically, Bunting believes that a primary focal infection may be determined in each case. The disease seems uniformly to run a fatal course.

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i. Hodgkin's Disease

(Infectious Granuloma, Malignant Granuloma, Generalized Lymphadenoma, Malignant Lymphona)

Definition.—A disease characterized by an infectious granulomatous process, involving especially the lymphadenoid tissue of the body, and associated with the presence in the lymph glands (1) of characteristic

histological lesions (fibroblasts, giant cells, eosinophils), and (2) often of a cultivable, pleomorphic, diphtheroid, Gram-positive, non-acid-fast bacillus, the *Corynebacterium granulomatis maligni.*

Etiology.—The bacterial agent that possibly causes the disease has already been referred to above. E. E. Irons cautiously emphasizes the fact that the evidence of a causal relationship is not yet convincing, though it is strong. We now know how often bacteria may be present in the

Fig. 313.—Hodgkin's Disease, Unilateral. (Med. Service, J. H. H.)

lymph nodes as accidental inhabitants, and it is possible, as Irons hints, that the diphtheroid bacillus is such an accidental inhabitant.

Symptoms.—The onset is insidious, the patient as a rule noticing, first an enlargement of one side of the neck, which brings him to his physician. On examination the latter finds that the enlargement is due to swollen lymph glands. Subjectively, there may not have been much inconvenience, though in some cases a patient will complain of lowering of his bodily and mental powers, easy fatigability, dyspnea and palpitation on exertion, anorexia, and beginning emaciation. Itching of the skin is a

prominent early symptom in many cases, and various peculiar skin eruptions may be seen. While the lymph glands first to be enlarged are usually those of the neck, lymphadenoid proliferation may begin elsewhere (axilla, groin, spleen, mediastinum, etc.). Less often, the disease begins acutely. Most puzzling are the cases in which only the internal lymphadenoid tissues are involved; but sometimes, in these, the relapsing fever (Pel and Ebstein), so characteristic of many of the cases of the

Fig. 314.—Hodgkin's Disease, Bilateral. (Med. Service, J. H. H.)

disease, may give the clew to the diagnosis. The periods of pyrexia have been well described by MacNalty. After a period of fever of low grade, or of normal, or subnormal, temperature, there is a steady rise for from two to four days, when a temperature of 105° F. may be reached. The temperature remains at this level, usually for about three days, and then falls by lysis during another period of three days, after which it becomes subnormal. Then an afebrile period of ten days, two weeks, or more may occur, to be followed by another period of pyrexia. Such relapsing pyrexia may go on for months. Osler has described a case in which the pyrexia lasted exactly fourteen days in many successive paroxysms, the glands swelling and becoming hot and tender during the febrile period.

Trousseau divided the disease into three stages: (1) the latent period, (2) the progressive period, and (3) the cachectic period. It is often possible to make out these three stages of the disease, but it does not always follow this typical course. The glands of the neck may be involved for months, or even for years, before the other glands of the body become involved. When the mediastinal glands become enlarged, the signs of intrathoracic tumor (cough, dyspnea, cyanosis, dilatation of the veins of the thorax, etc.) develop. As the disease progresses, the patients become anemic, emaciated, and cachectic.

Summary of the Blood Findings.—Red Blood-corpuscles.—In the early stages, the number is unchanged, but later anemia develops, and toward the end may become of high grade A remarkable exception may

Fig. 315.—Hodgkin's Disease. Enormous Shadow, Marked by Arrows, Due to Enlarged Mediastinal Glands. (By courtesy of Dr. Baetjer and Dr. Waters; X-Ray Department, J. H. H.)

exist in the cases with large intrathoracic growths causing cyanosis and dyspnea; here, a dyspnoeic erythrocytosis may develop, the red count reaching six millions or more, with corresponding high hemoglobin-values.

Hemoglobin Content.—This corresponds to the number of red cells, or is relatively a little more reduced.

Color-index.—When anemia develops, the color-index is lower than normal.

White Blood-corpuscles.—The total count may, at first, be unchanged, though later there is usually a moderate increase, the count reaching from 10,000-30,000-50,000 leukocytes.

The differential count shows a normal or a high percentage of polymorphonuclear neutrophils. The eosinophils may show a diminished percentage in the early stages, though even then the absolute numbers are often increased. In some cases, there is an enormous increase in the eosinophils. In a patient of mine showing a high total white count, over 60 per cent of all the white cells were eosinophils. The lymphocytes are usually decreased, both in percentage and in absolute numbers. Occasionally myelocytes are present.

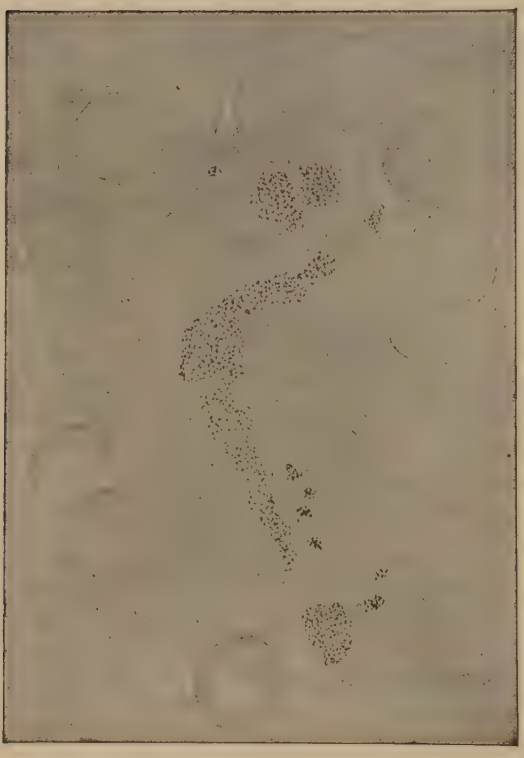

Fig. 316.—Blood Platelets and Detached Pseudopodia of Megalokaryocytes in Smears of the Peripheral Blood in Hodgkin's Disease. (After C. H. Bunting, J. H. H. Bull.)

A striking feature often seen in the early stages, is a large number of large mononuclears and especially of transitional forms. Bunting has especially emphasized the presence of a large number of transitional forms, and thinks that he can make the differential diagnosis, in doubtful cases, by the blood smear. In our experience at the Johns Hopkins Hospital, transitionals have been very numerous in the blood of Hodgkin's cases. It is not uncommon to find 7-10 per cent, or more, of the total count made up of transitionals. An occasional n-myelocyte may be seen. The total count of white corpuscles is not always increased in Hodgkin's disease; it may even be diminished, at least at certain periods.

Blood Platelets.—These are often markedly increased, and in addition, pseudopodialike masses, due to pinching off from the protoplasm of megalokaryocytes, are often visible in smears made from the blood (Bunting).

Prognosis.—The duration of the disease varies greatly in different cases. Spontaneous remissions are not infrequent, and, now that we have learned how to utilize the x-rays, arsenic, and autogenous vaccines (Billings and Rosenow), long periods of remissions can be maintained; whether a complete cure can ever be brought about is not yet certain.

Acute cases occur in which the disease progresses rapidly to a fatal termination within a few months. On the average, the disease lasts two or three years, but I have patients under observation who have lived much longer, and are still living. Remarkable changes in the size of the glands occur spontaneously, and under treatment.

Bunting and Yates are now testing immunizing methods in conjunction with surgical therapy.

Diagnosis.—The essential points are the following: (1) signs of hyperplasia of the lymphadenoid system; (2) absence of a leukemic blood-picture; (3) presence of a neutrophilic leukocytosis, of an eosinophilia, and of a remarkable increase in the transitionals; (4) typical histological lesions (Dorothy Reed) in a lymph gland excised for diagnosis; and (5) growth of a diphtheroid bacillus in cultures made from an excised gland.

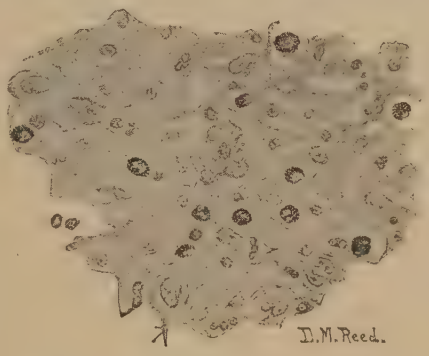

Fig. 317. — Characteristic Histology of Hodgkin's Disease, Swollen "Endothelial" Cells Are Seen Lying on the Fibrils of the Reticulum. In the Interstices of the Stroma are Found Lymphocytes, Eosinophils and Large Epitheloid Giant Cells. (After Dorothy M. Reed, J. H. H. Reports.)

Differential Diagnosis. — (1) From *leukemia* (blood picture). (2) From *tuberculosis of the lymph glands* (histological examination of excised gland, tuberculin reaction, tendency of glands to coalesce and to break down, absence of Hodgkin's blood-picture, culture from lymph gland. It must be remembered, however, that not a few cases of Hodgkin's disease are complicated by tuberculous infections toward the end); (3) From *aleukemic lymphadenosis* (histological examination, culture from lymph glands, absence of Hodgkin's blood-picture; lymphopenia); (4) From *lymphosarcoma* (usually larger tumor, invading adjacent structures, histological picture, blood picture); (5) From *syphilis* (sections, and culture, from lymph gland, Wassermann reaction).

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ii. Tuberculosis of the Lymph Glands
(*Tuberculous Lymphadenitis*)

Several forms of tuberculosis of the lymph glands occur. In one form —generalized tuberculous lymphadenitis—all the lymph glands of the body are involved, and the clinical and histological picture may, for a time, closely resemble that of aleukemic lymphadenosis.

Again, the so-called "scrofula" of children and of young adults is, in most cases, due to tuberculous infection of the cervical lymph glands.

The commonest form of lymphgland tuberculosis in young children is tuberculosis of the bronchial glands.

Diagnosis of Tuberculosis of the Cervical Lymphglands.—We have to rule out (1) Hodgkin's disease; (2) aleukemic lymphadenosis; (3) lymphosarcoma; (4) exudative diathesis (Czerny); (5) simple adenitis secondary to chronic nasopharynygitis (infected adenoids and tonsils); and (6) syphilis of the lymph glands.

In advanced cases, the diagnosis is easy. The glands are large, become matted together, and often soften and break down, with abscess, or fistula formation. Secondary infections with pyogenic organisms are not uncommon.

If one consider the state of the patient as a whole, the exact condition of the individual lymphglands, the blood picture, and the results of tuberculin and Wassermann tests, there should be but little difficulty in arriving at a correct diagnosis.

Diagnosis of Tuberculosis of the Bronchial Glands.—This may be exceedingly difficult to make sure of, even when we suspect its existence. If the child, hitherto healthy, gradually grows weak and anemic, loses

its appetite, ceases to gain in weight, begins to show an irregular fever, and especially if it develop a cough not unlike that of pertussis and an expiratory dyspnea, we must strongly suspect the existence of a bronchial-gland tuberculosis. There is usually tachycardia and some dyspnea. If the masses become large, there may be signs of compression of the N. recurrens, of the cervical sympathetic, of the trachea, or of the innominate vein.

Swelling of the paramammillary or of the thoracic lymphglands, and tenderness on percussion of the spines of the second to the seventh thoracic vertebrae are not uncommon. Relative dullness over the fifth and sixth thoracic vertebrae may be found when the glands at the bifurcation of the trachea are enlarged (de la Camp). On auscultation, bronchial breathing over the spines from the fifth and sixth thoracic vertebrae downward may be present. Normally, the breathing there is vesicular, or at most bronchovesicular. Carefully taken röntgenograms of the thorax may reveal enlarged bronchial glands, especially if calcification has taken place in parts. Tuberculosis of the glands elsewhere, especially of the supraclavicular glands, may be helpful in arriving at a decision. In young children a positive von Pirquet's reaction favors the diagnosis. As Harold Parsons emphasizes, it is important to make the diagnosis early, before the signs have become outspoken.

The dangers of bronchial-gland tuberculosis should always be kept in mind; it is not infrequently the starting point of a tuberculous meningitis, or of a miliary tuberculosis.

Diagnosis of Tuberculosis of the Mesenteric Glands.—This condition, known in the older bibliography as *tabes mesenterica*, is much less common than tuberculosis of the bronchial glands. The disease presents itself as a slowly developing cachexia, with irregular fever, and diarrhea. Sometimes it is possible to palpate the enlarged glands, but this is usually difficult or impossible on account of meteorism. Extensive tuberculosis of the mesenteric glands may go on without symptoms for a long time.

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iii. Syphilis of Lymph Glands

The diagnosis is usually easy by means of the history, by the Wassermann reaction, and, when in doubt, by histological examination of one of the glands to rule out other forms of lymphoma.

Glandular enlargement in syphilis is more commonly generalized. The epitrochlears, the occipitals, and the glands of the anterior axillary chain are frequently involved; non-syphilitic glandular diseases very seldom affect these glands. In syphilis the enlargement of the glands is usually only moderate; but the increased consistency, which makes them readily palpable, gives them a characteristic "shotty" feeling. In the glandular group that receives the lymphatic drainage from the primary lesion it is the rule to find one or two markedly enlarged glands that are characteristically painless.

2. The So-called Leukemoid Diseases

Under this heading are included (a) lymphosarcomatosis, (b) the chloromata, and (c) the myelomata.

(*a*) *Lymphosarcomatosis* (*Kundrat*)

Here we have to deal with a very peculiar affection, which seems to stand mid-way between generalized aleukemic lymphadenosis and genuine malignant sarcoma.

The disease begins locally, but quickly spreads to all the lymph glands in the region in which it begins through the rapid formation of metastases by way of the lymph channels. Some have even regarded it as a "system disease," like the leukemic and the aleukemic lymphadenoses. Its resemblance to true sarcoma is shown by its disrespect for gland boundaries, but it does not invade neighboring organs in the destructive way characteristic of true sarcoma.

This disease may begin in any part of the lymphadenoid apparatus (cervical glands, mediastinal glands, tonsils, intestine, spleen). There is a marked tendency to extension of the process along the sheaths of the blood vessels and nerves. In one of my patients, the whole vena cava was surrounded longitudinally for a long distance. This had caused narrowing of the lumen and partial venous obstruction.

In the blood the red cells are diminished, especially as the disease advances. The white blood-corpuscles are usually increased in number, owing to a neutrophilic leukocytosis, and there is sometimes a marked lymphopenia. The blood findings are, however, not at all characteristic.

I am personally inclined to look upon this disease as an especial form of Hodgkin's disease, though the proof of this has yet to be brought, and the histological findings differ somewhat.

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(*b*) *Chloromata*

Here we stand before a group of diseases that are much more closely related, in my opinion, to the leukemias than to true tumors. The chloromata represent generalized "system diseases" affecting either the lymphadenoid tissue throughout the body, or the myeloid tissue. The blood picture and the clinical course resemble very closely those seen in the acute leukemias, and I regard the designation chloroleukemia as very appropriate. We separate the chloroleukemias from the other leukemias, however, (1) on account of the green color of the chloromatous proliferations (also seen in the layer of leukocytes of centrifugalized blood when the chloroma is accompanied by leukemic blood-changes, Jacobaeus), and (2) on account of the destructive growth of the chloromatous proliferations, these tumors sometimes invading adjacent bones like malignant neoplasms.

It is often impossible to separate the chloroleukemias during life from the other acute leukemias, as fever is present and a hemorrhagic diathesis quickly develops, though if multiple sub-periosteal tumors be present, especially at the sites of predilection (orbit, bones of the skull, vertebrae, ribs), the diagnosis can sometimes be made. Especially characteristic are the cases with orbital chloromatous masses causing exophthalmos.

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(*c*) *Myelomata*

Definition.—A disease in which circumscribed or diffuse tumorlike hyperplasia of the bone-marrow tissue occurs, associated in most cases with Bence-Jones protein in the urine. The blood picture is non-leukemic. The disease can be regarded as a form of myeloid adenosis, but its neoplastic nature is indicated by its destructive tendency, and by the occurrence of metastases.

A myeloma may arise from any one of several of the tissues in the marrow. The commonest form is that consisting of myeloblastlike cells (erroneously designated "lymphocyte-myeloma"); less common are the forms in which the predominant cell resembles a myelocyte, or a plasma cell; in one instance the predominant cell resembled an erythroblast (erythroblastoma of Ribbert). Strange to say, the first case described by Kahler was not a true myeloma at all, but an endothelioma (Hirschfeld).

Symptoms.—The patient complains at first of neuralgic pains. If a routine urine-examination be made, the physician will be surprised to find the characteristic Bence-Jones body (precipitation at 50° C., dissolving on heating further). It must be remembered, however, that Boggs and Guthrie have shown the presence of Bence-Jones body occasionally in myeloid leukemia, and, moreover, Bence-Jones protein is not constantly present in myeloma.

As the disease advances, metastases may become evident as painful swellings on the ribs or in the skull, and spontaneous fractures may occur. X-ray examinations of the bones are very helpful in differential diagnosis.

The blood findings are not characteristic. There may be neutrophilic leukocytosis, with here and there a myelocyte present (Arneth). The absence of a leukemic blood-picture is important.

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E. Diseases Characterized by Disturbances in the Coagulability of the Blood

(*The Hemorrhagic Diseases*)

In many different diseases, a hemorrhagic tendency may develop; thus, in a whole series of infectious diseases, especially septic processes (yellow fever, measles, typhoid, and diphtheria), it is common to have hemorrhagic complications. Again, in the severe anemias, and in the leukemias, a hemorrhagic diathesis very often develops. But there is an especial group of diseases in which a hemorrhagic tendency is the essential feature; in this group belong hemophilia, the various forms of purpura, scurvy, Barlow's disease, and essential hematuria.

Various attempts have been made to classify these hemorrhagic diseases. Recently, Whipple and Moss have drawn attention to a possible etiological classification, according as the disturbance of coagulability depends upon various factors concerned in blood coagulation (fibrinogen, calcium, prothrombin, antithrombin, blood platelets, fibrin-dissolving ferments, etc.). Undoubtedly this is a logical method of classification, and it is to be hoped that our knowledge of these obscure diseases, now in rapid growth, will soon become sufficient for a classification of this sort; but at present an attempt to separate the diseases in which the hemorrhagic tendency depends upon a deficiency of prothrombin from those in which there is an excess of antithrombin, or those in which there is deficient fibrinogen, and so on, would be premature.

Certainly fibrinogen is diminshed in intoxications that injure the liver, and Whipple suggests that the hemorrhagic symptoms of acute yellow atrophy, and of yellow fever, are referable to the decrease in the fibrinogen of the blood. The tendency to hemorrhage in cirrhosis hepatis may have the same origin.

There does not seem to be any evidence favoring the view that a diminished calcium-content in the blood is responsible for hemorrhagic tendencies, though it must be admitted that, in icterus, the delay in coagulation time may depend upon an interference with the activity of calcium, owing to its union with bile pigment.

It seems probable that a diminution in the prothrombin-content of the blood, however, may sometimes be of definite importance. Whipple states that in the "hemorrhagic disease of the new-born," prothrombin may disappear from the circulating blood; though present at birth, it vanishes in these cases during the first few days of life. According to W. H. Howell, the prothrombin-content of the blood plasma is diminished in hemophilia. An excess of antithrombin has been found in the blood in some cases of sepsis and of miliary tuberculosis (Whipple). There may also be an excess of antithrombin in the leukemias and in the grave

anemias, especially in aplastic anemia. In some cases of disease of the liver with jaundice, an antithrombin excess has been demonstrated.

It seems probable that the number of blood platelets may be an important factor, though just how their presence is essential is only now being worked out (Duke).

The occurrence of fibrinolytic ferment may sometimes be responsible for immoderate hemorrhage; though clots form, they are not permanent, owing to softening from fibrinolysis. Goodpasture has shown that this ferment may be present in small amounts in the blood in hepatic disease. The normal blood-plasma contains a ferment that can inactivate fibrinolytic ferment.

Little or no work has as yet been done upon the significance of deficient thromboplastin-formation. I shall not be surprised if, later on, an incapacity for adequate thromboplastin-formation should be demonstrated, in general, and in local, hemophilia. This is only a guess, but the subject would seem to be well worth investigation.

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1. Hemophilia

Definition.—A constitutional condition in which there is a congenital tendency to hemorrhage that persists throughout life; it occurs in families in which the men are "bleeders" and do not transmit the disease and the women, though they do not bleed themselves, transmit the tendency to hemorrhage to their sons.

Occurrence.—Bleeding families are known in every country, though they seem to be more common among the Germans than among other nationalities. How a bleeding family becomes started, we do not know, but, once begun, a part of the men bleed, though their offspring are not bleeders. The women, as a rule, do not bleed, but their sons do. The women, therefore, are called "conductors" of the disease. There seem to be occasional exceptions to the rule, but rarely.

An excellent account of the inheritance of hemophilia is to be found in the monograph of Bulloch and Fildes (1911). The mode of transmission seems to be similar to that in hemeralopia and in Daltonistic families.

According to Grandidier's statistics (1877), 93 families of bleeders are known in Germany. Among these, 258 members, of whom only 22 were women, suffered from hemophilia.

Nature of the Disease.—Everything indicates a Mendelian heredity as being responsible for the disease, but in what this Mendelian unit consists we as yet have no idea. Most authors seek it in some disturbance of coagulation of the blood.

Certainly the coagulation of the blood is slowed in hemophilics. This slowing is not due to any deficiency in fibrinogen. According to W. H. Howell there is, however, a diminution of prothrombin. There does not seem to be an excess of antithrombin, though it would seem to me to be possible that there may be insufficient thromboplastin formation to counteract a normal amount of antithrombin. The subject might well be investigated from this side. In case there should be found a deficient formation of thromboplastin, the cause might lie in a Mendelian inheritance of deficient thromboplastin-forming power in the protoplasm of the cells of the walls of the blood vessels, either throughout the body, as in general hemophilia, or in a local area, as in regional or local hemophilia. This possibility, which I throw out simply as a tentative suggestion in the hope that it may stimulate experimental work, would be in accord with Sahli's hypothesis of a fermentative inferiority of the protoplasm of the body in hemophilia.

Morawitz feels certain that, in addition to the disturbances of the coagulability of the blood, there must be an abnormal fragility, or permeability, of the vessels themselves. He also hints that an absence, or deficiency, of the agglutination of the blood platelets may play a rôle in hemophilia.

The best account of the factors of coagulation in hemophilia available at present will be found in Howell's article.

Symptoms.—Hemophilia usually makes itself noticeable in early infancy. Sometimes the bleeding from the umbilical cord is abnormally prolonged; in other children, alarming hemorrhage may develop at the time the teeth are first cut, or upon circumcision, or on piercing the ears for ear-rings. Some children, however, show no hemorrhagic tendency until later childhood (tooth extraction, minor operations). Occasionally, the tendency is first seen on minor injury, when at play, or from a whipping at school.

The degree of hemorrhagic tendency varies greatly. Some bleeders reach a ripe old age, the tendency growing less with advancing years. Many bleeders, however, die in early childhood.

The members of bleeding families are usually of feeble constitution, with gracile bony framework, and delicate white skin; they are usually thin and pale. The ordinary blood-examination may be normal, except after the hemorrhages, when, of course, the blood shows the signs of a posthemorrhagic anemia. It is remarkable how quickly bleeders regenerate the blood lost during the hemorrhages.

The hemorrhages in bleeders may arise either after trauma or spontaneously, and the hemorrhage may occur in any part of the body, most often from the mucous membranes (mouth, nose, intestines.) If a patient be known to come from a bleeding family, one must be cautious even in taking a drop of blood for microscopical examination, and operations of all sorts, even minor operations, must be avoided, except where they are absolutely imperative.

Hemarthros is a common complication in hemophilia. It may affect any joint, though the knee is most often attacked. The findings in the joint on x-ray examination are very characteristic, the expert being able to make the diagnosis simply from the x-ray plate.

While most bleeders suffer from general hemophilia, there are some bleeders that bleed only in certain regions of the body; thus one form of essential hematuria seems to be due to local hemophilia; but there are other forms of essential hematuria, and one dare not make the diagnosis of hemophilia except in bleeding families.

It is no wonder that the Eugenics Record Office has taken up the study of hemophilia. Obviously, the women of bleeder-families, though unaffected, should never marry, or, if they marry, should not have children. There would seem to be no reason for excluding the men from marriage, except in the very rare families in which the men transmit the disease.

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2. The Purpuric Diseases

Under this heading will be included the various forms of purpura, including (1) *purpura simplex,* in which the hemorrhages are limited to the skin and subcutaneous tissues, (2) *purpura hemorrhagica,* or *morbus*

maculosus Werlhofii, in which there are hemorrhages of the skin and mucous membranes; (3) *peliosis rheumatica* (*Schoenlein*), in which there are cutaneous hemorrhages associated with joint diseases (often hemarthros); (4) *purpura abdominalis* (*Henoch*), in which there are cutaneous and intestinal hemorrhages and joint pains; and (5) *purpura fulminans* (*Henoch*), in which there are only cutaneous hemorrhages, but the course is rapid and the disease quickly fatal.

Morawitz considers all these diseases as different manifestations of one and the same process, which he designates as morbus maculosus Werlhofii. The dis-

Fig. 318.—Purpura hemorrhagica. (Med. Clinic, J. H. H.)

ease can be easily distinguished from hemophilia, for in the latter there is a permanent tendency to hemorrhage, and the disease is hereditary. In the purpuric diseases, the condition is temporary, and there is no hereditary factor. It is easy also to exclude scurvy (epidemic or endemic character; definite relation to one-sided diet; markedly spongy gums with loosening of the teeth). The purpuras under consideration may sometimes, however, be confused with the hemorrhagic tendency developing in septic and other infections, and with that developing in acute leukemia, or in the aleukemic lymphadenoses and myeloses.

These purpuric diseases may occur at any age, but are commonest in middle life, women being more often affected than men. The coagulation time of the blood is often delayed, the conditions resembling those in hemophilia. Duke reports a great reduction in the number of platelets in cases

of hemorrhagic purpura that he has studied. Howell could find no disturbance of the prothrombin-antithrombin balance in the purpuric diseases. It would seem to me that thromboplastin formation should be studied here also. It is interesting that the injection of fresh human serum and of normal rabbit's serum is often of prompt benefit in these cases (W. L. Moss).

In the **hemorrhagic disease of the new-born** not associated with syphilis or sepsis (Holt), and not due to hemophilia, we seem to have to deal

Fig. 319.—Post-mortem Photograph of a Case of Purpura fulminans, Showing Symmetrical Distribution of Purpuric Areas and Gangrene of Toes. (After C. A. Elliott, Arch. Int. Med.)

with a special form of purpura. Moss suggests that we designate it morbus maculosus neonatorum. Whipple has studied two of these cases, the blood, in both, showing a marked delay in coagulation time, and a complete absence of prothrombin. Transfusion of blood and serum injections have yielded most gratifying results in these hemorrhages in the new-born. Undoubtedly many a life has been saved by the intravenous injection of a little fresh human serum or by subcutaneous injection of whole blood. Goodpasture has had success from subcutaneous injection of pure thrombin prepared by Howell's method. If a large amount of blood has been lost, an immediate transfusion of whole, or of defibrinated, blood should be resorted to. The amount should not exceed 200 c.c. (Moss).

Evarts Graham of Chicago believes that hemorrhagic disease of the new-born may be due to injury to the liver secondary to the chloroform anesthetic administered to the mother during labor.

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3. Scorbutus (Scurvy)

Definition.—A form of acquired hemorrhagic disease occurring in epidemics, due to a faulty food-intake, and independent of hereditary influences.

History.—Formerly, many large and fatal epidemics occurred, especially in armies and on vessels at sea. In the well-known expedition of Lord Anson, in the middle of the 18th century, no less than 380 out of 500 sailors died of scurvy. Now that the way of preventing the disease is known, it is rare to have any large outbreak. The writer when returning from Europe a few years ago (1911) saw a sailing vessel in distress on which nearly 30 passengers (Society of Holy Ghosters) had been for many days without any food, and for a longer period with improper food. Our vessel gave them a supply, but many of them had already developed scurvy, and when they arrived in America many of them died of the disease. The disease is still prevalent in some parts of Russia, where many of the peasants live under unfavorable conditions, especially during the long fasting-period in the spring.

Etiology.—The disease appears to depend upon a lack of something that is present in normal food. When people eat plenty of vegetables, especially of green vegetables and potatoes, they do not develop scurvy, but if they live chiefly upon meat, and especially upon salt pork, scurvy is prone to develop. In the army and navy, provision is now always made for a supply of lime juice or of lemon juice, which is strongly antiscorbutic.

Just what substance is present in antiscorbutic foods that is absent in the foods of people that develop scurvy is not yet known. Garrod attributed the development of the disease to impoverishment of the body in potassium. More recent studies make it seem probable that scurvy depends upon the lack of one of the vitamines, though the vitamine doctrine is not yet as firmly established as we could wish.

Many believe that scurvy is an infection, and that lack of proper food predisposes to the infection. The proof of an infectious nature has not yet been brought. Scurvy may occur at any age. Some people do not develop scurvy, even when the diet lacks vegetables. Thus the Esquimaux live largely upon fat and meat and rarely develop scurvy. In the Nansen polar expedition, both Nansen and Johannsen lived for months almost entirely upon meat and fat, but neither became scorbutic.

Symptoms.—In the prodromal stage the patients feel weak, drowsy and chilly, and complain of rheumatic pains. Sometimes they suffer from night-blindness (hemeralopia). Very soon, the gums become spongy and sore at the margins of the teeth. The breath becomes foul, the saliva is increased, and soon a hemorrhagic diathesis develops, the spongy gums bleeding, often profusely; as the stomatitis develops, the spongy tissue of the gums becomes elevated, swelling up around the teeth, so as to make mastication painful. In severe cases, actual necrosis of the gums and ulceration may occur; the teeth may grow loose and fall out. Sometimes the alveolar process becomes necrotic.

Among the other signs of hemorrhagic diathesis in scurvy, subcutaneous hemorrhages must be mentioned. The hemorrhages are small at first, beginning around the hair follicles, but later, they may become very large and confluent. Hemorrhage also occurs into the muscles, especially the muscles of the calves, and into the joints (hemarthros); sometimes there are sub-periosteal hemorrhages in adults very much like those in Barlow's disease in children. The patients show irregular fever after the hemorrhages develop. Hemorrhages may occur from the mucous membranes (epistaxis, menorrhagia, enterorrhagia), but they are less common than in other forms of hemorrhagic diathesis.

The patients emaciate, owing to inability to eat. In the severer forms, outspoken cachexia develops.

As a result of the hemorrhages and of the malnutrition a secondary anemia develops, with neutrophilic leukocytosis. If nucleated reds are present, they are usually normoblasts. The color-index is lower than normal.

Prognosis.—In the mild cases, and often in those of considerable severity, cure will be effected if the diet be corrected. But in the severer cases, even when proper food is given, death may ensue. In the cases that recover, convalescence is often prolonged.

Diagnosis.—This is easy in epidemics, when scurvy can be recognized in its early stages, but in sporadic cases there may be considerable diffi-

culty in recognizing the nature of the disease, though the occurrence of stomatitis with hemorrhagic diathesis in a family of non-bleeders, and in the absence of a leukemic blood-picture, makes the diagnosis probable. Acute septic processes are usually easy to rule out, especially if a blood culture be made. In the hemorrhagic diathesis due to sepsis, there is usually high fever and the stomatitis is rarely of as severe a grade as in scurvy.

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4. Barlow's Disease

(*Infantile Scurvy*)

Definition.—A hemorrhagic disease occurring in children, most often at the end of the first or at the beginning of the second year of life, characterized by slow development, pains, especially in the lower part of the thigh on movement of the lower extremities or on pressure, and palpable swelling, due to hemorrhages under the periosteum of the femur.

Symptoms.—In children, especially in those that have been fed upon sterilized milk, the symptoms slowly develop; the child shows signs of pain, or discomfort, whenever the lower extremities are moved, or whenever the lower part of the femur is pressed upon. In more advanced cases, there may be hemorrhages beneath the periosteum of the tibia, or of the bones of the forearm. As a rule, the joints are unaffected. Sometimes there are hemorrhages beneath the periosteum of the bones of the skull, or of the orbit; in the latter case, exophthalmos may result. If there be effusion of blood into the loose tissues of the eyelids, the child may develop black eyes, which, in association with the extreme pallor of the face, is very alarming to the family. One child suffering from Barlow's disease was brought to me on account of ceasing to walk after it had begun to do so. The parents thought it was paralyzed. On examination, the nature of the disease soon became evident, and on correction of the diet the child made a good recovery.

In some cases, the gums are spongy and bleed, though the stomatitis is rarely of the grade seen in scurvy. Cutaneous and subcutaneous hemorrhages may occur, in addition to the subperiosteal hemorrhages, but it is

the predominance of the subperiosteal hemorrhage that characterizes the clinical picture. According to Morawitz, renal hemorrhages (hematuria) are met with in 10 per cent of the cases.

After hemorrhages occur, the blood shows the signs of a "secondary," posthemorrhagic, anemia.

Prognosis.—Most children recover, provided the condition is recognized in time and a proper diet instituted. If fresh, unheated milk be given, recovery quickly occurs.

In cases that go too long without being recognized, the hemorrhages may become very severe and the child may die of anemia, or of cachexia.

At autopsy, besides the subperiosteal hemorrhages, there are peculiar histological changes in the bones. The bone-marrow is partly transformed into embryonic connective tissue, and there is an arrest of the endochondral and perichondral ossification. Pathologists look upon the bone disease as primary and the hemorrhagic disease as secondary (Schmorl, Nauwerck and Schoedel).

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5. Essential Hematuria

A form of hematuria known as essential hematuria has been described by Albarran, and by Senator. It is a term applied to hematuria of undiscoverable origin. Hematuria is, as a rule, due to (1) nephritis, (2) nephrolithiasis, (3)

renal tumor, or (4) tuberculosis of the kidney. These conditions must, of course, be ruled out. We have referred above to the hematuria that is an expression of local hemophilia, occurring in families of bleeders, but in these cases the hereditary influence is diagnostic. In the absence of any of the known causes of hematuria, and in the absence of hemophilia, the diagnosis of essential hematuria may be made. Its nature is not yet understood. Physicians that meet with it, should make it a point, if possible, to have studies made of the different factors concerned in the coagulation of the blood.

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F. Diseases, Other Than the Hemolytic Anemias, in which Hemolytic Phenomena are Prominent

We have described above the group of hemolytic anemias. We shall consider here (1) paroxysmal hemoglobinuria, (2) snake poisoning, and (3) black-water fever.

1. Paroxysmal Hemoglobinuria

Definition.—A rare condition, characterized by periodic attacks in which oxyhemoglobin and methemoglobin are excreted in large quantities in the urine.

Etiology.—Men are more often attacked than women. The actual exciting cause of the single attack appears to be exposure to cold. The presence of hemolytic amboceptors in the blood can be demonstrated, but the origin of these is not clear. In many cases, a syphilitic infection has preceded the development of the disease.

Symptoms.—The onset of an attack can often be recognized by patients that have suffered from previous attacks. After exposure to cold, they begin to feel chilly, become febrile, complain of pains in the small of the back, and of paresthesia in the extremities. Soon afterward, the dark red, or brownish, urine is passed. In patients that suffer from this disease, an attack can often be brought on by immersing the hands or feet in cold water. The attack passes off within 24 hours, the urine quickly becoming

free from hemoglobin, though urobilin may continue in the urine for some little time after the attack.

In severe attacks, the number of red corpuscles per cubic millimeter may be diminished by as many as a million cells, though during the actual attack this may not be evident on account of temporary concentration of the blood through vasomotor changes. The shadows of red blood corpuscles may, however, be visible, along with poikilocytosis, in the fresh blood preparation made during an attack. Morawitz has observed normoblasts and myelocytes in the blood after an attack, the breaking down red corpuscles stimulating not only the erythropoietic, but, apparently, also the leukopoietic tissue of the bone-marrow.

The coagulation time during an attack is shortened, but fibrinolytic ferment is abundant and the clot formed often re-dissolves quickly. It is interesting that attacks of paroxysmal hemoglobinuria can occur with patients that suffer from polycythemia rubra (Pels). Sometimes there is a marked reduction in the number of lymphocytes and of the eosinophils in the blood during an attack (Meyer and Emmerich).

If blood be drawn during an attack and allowed to clot, the serum is often stained red, due to hemoglobinemia. Normal serum does not contain free hemoglobin. In the intervals between attacks, hemoglobinuric patients may show albuminuria without any increase in arterial tension.

Nature of the Disease.—The relation to syphilis is interesting, since syphilis is due to a protozoön parasite and hemoglobinuria is known to occur in other protozoön invasions: namely, in the piroplasma disease of horses, and in malaria (see Black-water Fever). This point has been especially emphasized by E. Meyer.

An autolysin, that is, a hemolysin capable of laking the patient's own corpuscles, has been demonstrated in the blood of hemoglobinurics by Donath and Landsteiner. This autolysin consists of two parts: an amboceptor, which is moderately thermostable; and complement, which is thermolabile. The important observation was made that this amboceptor unites with the red corpuscles only at low temperatures. Hoover of Cleveland has, in this country, made especial studies of this henfolysis.

It has further been shown that during an attack all of the patient's complement may be used up. If a test tube experiment be made at such a time with the patient's blood, exposure to cold causes union of the amboceptor with the red corpuscles, and on warming again no hemolysis takes place because no complement is present; but if a little fresh serum be added from a normal person, hemolysis will occur owing to the addition of complement in the foreign serum.

The explanation given above properly accounts for the hemoglobinuria in many cases, but other cases have been described in which men that have earlier had lues have this autolysin in the blood, though they never suffer from attacks of hemoglobinuria. Again, hemoglobinuric patients are known, whose attacks are not brought on by exposure to cold, but by violent muscular exercise, or by emotional excitement. The whole subject is now under investigation, and before long we shall doubtless have fuller information regarding the different varieties of hemoglobinuria.

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2. Snake Poisoning

Snake-venom is actively hemolytic. The early studies of Weir Mitchell on rattle-snake venom, and recently the studies of Kyes on cobra-venom, drew widespread attention to this form of hemolysis. According to Kyes, lecithin is the activator of the snake-venom, uniting with it to form a toxic cobralecithid. Some years ago, when working on snake-venom myself, I was greatly impressed with the rapidity with which extensive lesions throughout the body can be produced in experimental animals. Within half a minute after injection into the ear-vein of a rabbit, extensive ecchymoses in the serous membranes can be seen.

Many animals (insects, fishes and reptiles) produce hemolytic poisons. While snake-venom is the best known, the poisons of scorpions and of bees have also been studied.

These hemolysins of animal origin have their analogues in the saponins (Kobert) of vegetable origin. Saponins are hemolytic in solutions of very feeble

concentration (1:125,000). Here, too, lecithin favors the hemolysis, while cholesterin inhibits the hemolytic activity. The poisoning due to morchella is known as helvella acid. It is powerfully hemolytic in its effects, causing fever, jaundice, hemoglobinemia and hemoglobinuria. The poison is soluble in boiling water, so that if the morchella be first stewed and the water poured off, they are no longer poisonous.

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3. Black-water Fever

In certain severe cases of malarial infection, hemoglobinuria occurs (black-water fever). By some it has been supposed to be due to the action of large doses of quinin, but it seems more likely that it is due to the malarial invasion itself. Just why some cases of malaria and some cases of syphilis are associated with hemolysis and hemoglobinuria and others not is as yet a mystery.

Brem distinguishes (1) a "pernicious malaria with hemoglobinuria" from (2) an "erythrolytic hemoglobinuria" but inclines to the belief that both forms are due directly to a hemolysin produced by the malarial parasite, usually the estivo-autumnal variety. Lovelace maintains (1) that blackwater fever is not due to a particular species of malarial parasite, and (2) that the administration of quinin, in large or small doses, was, in his series, an invariable antecedent of the hemoglobinuric condition. According to Cardamatis, the mortality in cases of black-water fever treated with quinin is 23.6 per cent while in cases treated without quinin it is only 7.5 per cent.

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G. Diseases of the Spleen

(*The Splenopathies*)

1. Introduction; Physiology and Pathology of the Spleen

The *methods of examining the spleen* have already been described.

The *physiological functions of the spleen* are still obscure. The organ is not essential to life, as many people get on well after total splenectomy, even when there is no evidence that accessory spleens exist.

It is known that the spleen is the principal organ for the phagocytosis, and the gradual disintegration, of senile or injured red blood corpuscles and also of the leucocytes. In lower animals and in man in pathological conditions this function may be largely taken over by the Kupffer cells of the liver (P. Kyes). In a remarkable case of grave anemia with lymphocytosis, which I studied some years ago, phagocytosis of red corpuscles and of lymphocytes was actively carried on by the Kupffer cells and by the endothelial cells of the liver capillaries as well as by the macrophages of the spleen.

In other words, the spleen and the liver act as purifiers of the blood. It may be that the hyperglobulia that sometimes follows splenectomy is due to the longer duration of life permitted to some of the red corpuscles in the absence of a spleen.

The Malpighian follicles of the spleen belong to the general lymphadenoid tissue of the body and are therefore concerned in the production of lymphocytes.

The *relation of the spleen to iron metabolism* is of considerable interest. It is probable that the iron removed from the red corpuscles by macrophages is again utilized for the manufacture of new corpuscles in the bone-marrow, but just how this iron is transferred to the bone-marrow is not known. According to Asher and Grossenbacher, iron excretion (in dogs) is increased after splenectomy.

The *relation of the enlargement of the spleen to cirrhosis of the liver in Banti's disease* has led to the idea of the possibility of hepatic injury due to an intoxication originating in the spleen. The fact that splenectomy cures Banti's disease (in the early stages) favors this view.

Hypersplenia.—Eppinger (1913) has set up a syndrome that he calls "*Hypersplenie*," and which he thinks depends upon increase of the normal splenic function. With King he has shown that the jaundice often present in splenomegalics tends to disappear after splenectomy, and that a parallelism exists between hemolytic processes and high iodin number (content of the blood in unsaturated fatty acids). This iodin number falls after splenectomy, though the fat-content of the blood rises. These investigators found a high iodin number in the blood in pernicious anemia, in cirrhosis hepatis, in hemolytic icterus, and in cardiac stasis.

Eppinger believes that the study of the quantity of urobilin in the stool by the spectro-photometric method of Charnass is a measure of the number of red corpuscles destroyed in the body. He found high urobilin values in the Addison-Biermer type of anemia, in hemolytic icterus, in malaria, in lead poisoning, and in pneumonia, whereas he found low values in the anemia of cancer and in the posthemorrhagic anemias. The urobilin values become enormously reduced after splenectomy in hemorrhagic icterus and in pernicious anemia. According to Eppinger's experience, splenectomy can be of help in hemolytic icterus, in pernicious anemia, in Banti's disease, in cirrhosis of the liver, and sometimes in grave catarrhal icterus. It is Eppinger's opinion that hypertrophic cirrhosis of the liver depends upon primary disease of the spleen and that many hepatic diseases presumably primary in the liver, for example alcoholic cirrhosis, are influenced greatly by the function of the spleen, which is sometimes more, sometimes less, hemolytically active.

It is further believed that increase of the activity of the bone-marrow can act as a defensive mechanism against "hypersplenia." It is also possible that fibrosis of the spleen helps to counteract a hypersplenic tendency. Eppinger suggests that, when hemolysis is demonstrably increased splenectomy is indicated rather than stimulation of the activity of the bone-marrow.

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2. Enlargement of the Spleen

(*The Splenomegalies*).

We subdivide the splenomegalies into those developing rapidly (*acute splenomegaly*), and those developing slowly (*chronic splenomegaly*).

(*a*) *The Acute Splenomegalies*

These are seen in many of the acute infectious diseases (typhoid, pneumonia, acute malaria, relapsing fever, sepsis, ulcerative endocarditis).

The enlargement here is due partly to hyperemia, partly to acute hyperplasia of the spleen pulp. In some cases there are also infarctions of the spleen.

In these acute splenic tumors the spleen is soft, as a rule, and may change palpably in size from day to day. Sometimes a perisplenitis occurs, and in septic cases suppuration of the spleen. In malaria, even in the acute cases, the consistence of the spleen is usually firmer than in typhoid.

(*b*) *The Chronic Splenomegalies*

These are very common. Some of them follow infections or intoxications of known etiology; in others, the cause is obscure. Among the chronic splenomegalies may be mentioned (1) ague cake, (2) the splenomegaly of kala-azar, or tropical splenomegaly, (3) the stasis spleen, (4)

splenomegaly in syphilis, (5) tuberculosis of the spleen, (6) amyloid spleen, (7) echinococcus cyst of the spleen, (8) the splenomegaly of Banti's disease, (9) the splenomegaly of the Gaucher type, and (10) the splenomegaly of chronic (congenital) hemolytic jaundice.

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i. Ague Cake

In patients that have had numerous malarial invasions, a hard chronic enlargement of the spleen is sometimes found (ague cake). This may last for years after the malarial infection.

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ii. Chronic Splenomegaly of Kala-Azar (Tropical Splenomegaly)

This has been studied especially by Rogers, and by Zarfl and his associates. In more than half the cases the spleen extends below the level of the umbilicus, and the liver is also enlarged. The disease is described more fully in the section on infectious diseases. It is characterized by its protracted course, anemia, leukopenia, and irregular remittent fever, and by the presence of the Leishman-Donovan parasites in the leukocytes of the blood, or, in much greater numbers, in the cells of the spleen pulp, obtained by exploratory puncture of the spleen. This disease is endemic in tropical regions, especially in India, but it has been seen also in Sicily and in Italy.

iii. Stasis Spleen

In portal obstruction, no matter what its origin, a stasis spleen may be seen, due to passive congestion. If it continue long, a chronic indurative splenitis develops, with increase of the connective tissue framework, after which the spleen remains permanently enlarged. On palpation, it is hard, the surface is smooth, and the anterior margin rounded. It is often associated with ascites, and with signs of chronic passive congestion in other organs. Infarct of the spleen is not uncommon in association with it, though infarcts may develop in acute septic processes also, in which case the septic infarct may give rise to an abscess of the spleen. The arteries of the spleen are end-arteries.

iv. Syphilis of the Spleen

In syphilis a chronic enlargement of the spleen may be due either to gumma or to diffuse luetic splenitis. Syphilitic splenomegalies are very common in congenital lues; the spleen may reach an enormous size, filling up the whole left side of the abdomen (Wassermann reaction).

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v. Tuberculosis of the Spleen

Chronic tuberculosis involving the spleen is a rare disease, but it is sometimes met with and may cause very great enlargement. It sometimes occurs without evidence of tuberculosis of other organs. A careful clinical and pathological-anatomical analysis of this condition has been made by Winternitz.

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vi. Amyloid Spleen

Amyloid may affect the spleen either in the form of *sago-spleen* (involvement of the Malpighian follicles), in which case there is but little enlargement, or in the form of *diffuse amyloid* degeneration, involving especially the splenic pulp, in which case the spleen may become considerably enlarged and firm.

Amyloid spleen is met with especially in chronic pulmonary tuberculosis, more rarely in syphilis, in chronic dysentery, and in chronic suppuration of various sorts. It is usually associated with (1) an enlargement of the liver due to amyloid, (2) marked albuminuria (without many casts) due to amyloid kidneys, and sometimes (3) obstinate diarrhea due to amyloid intestine.

vii. Echinococcus Cysts of the Spleen

This is a rare condition. I have myself never had opportunity to study a case of it, though in countries where echinococcus is common, these cysts of the spleen may be occasionally observed. In 235 cases in which there was echinococcus of the abdominal organs, Finsen found the spleen involved in only two. The cysts are usually multiple. Occasionally a hydatid thrill can be felt. On exploratory puncture (Caution!), hooklets may be found in the fluid. Puncture should never be done unless one is prepared to follow it up, immediately, by laparotomy.

The diagnosis can sometimes be made by the complement-fixation test. The blood in echinococcus disease often shows an eosinophilia.

Cysts other than those due to echinococcus sometimes occur in the spleen. They may be due either to old hemorrhage or to dilatation of the lymph vessels (so-called lymph cysts and serous cysts).

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viii. Banti's Disease

(*Primary Splenomegaly with Secondary Cirrhosis hepatis, Primary Splenomegaly with Anemia*)

Here we approach one of the most important of the splenomegalies, a form in which early diagnosis is of extreme importance for the welfare of the patient, since, if a correct diagnosis be made in the early stage, splenectomy may be performed and complete cure result. Banti's disease

was formerly called "splenic anemia," but this term is now taboo, since under it formerly, a whole series of non-related diseases were grouped. We owe the recognition of this particular form of splenomegaly and its establishment on a firm clinical basis to the Italian investigator Banti. In America, it has been especially studied by Osler, in England by R. Hutchison, and in Germany by Senator.

Symptoms.—The disease develops in youth, or in middle age, without apparent cause. The spleen enlarges in the *first stage,* the enlargement gradually increasing. There may be no other symptoms at first, though, sooner or later, anemia develops, with the symptoms characteristic of anemia. The blood shows a diminution of the red blood corpuscles, a low color-index, and sometimes a leukopenia with relative lymphocytosis, though many cases show no marked changes in the white corpuscles. The liver may be slightly enlarged at this stage, though there is, at first, no jaundice. It is in this stage that, if possible, the disease should be recognized, and the spleen removed. This first stage may last for several years.

Fig. 320.—Child with Splenic Anemia—Banti's Disease. (Med. Clinic, J. H. H.)

Gradually the *second stage,* or so-called "transition stage," develops; the patient becomes jaundiced, and complains of gastro-intestinal symptoms. The patient begins to go down hill rapidly; the anemia rapidly increases; he loses weight, and grows cachectic.

The *third stage,* or "ascitic stage," is now entered upon. Ascites due to cirrhosis hepatis appears, the general cachexia becomes pronounced, and the patient often dies after an esophageal or an intestinal hemorrhage.

In cases that come to autopsy, fibrous induration of the splenic pulp and atrophy of the Malpighian follicles are found, along with a moderate grade of atrophic cirrhosis of the liver and sclerosis of the splenic veins, sometimes with thrombosis of these veins.

Nature of Banti's Disease.—It seems probable that the disease is primarily a disease of the spleen, leading to an intoxication that causes cirrhosis hepatis. Banti's disease is sometimes confused with primary

cirrhosis of the liver causing secondary stasis-spleen, or with chronic splenomegaly due to congenital lues. It is very important not to confuse it with myeloid leukemia, for splenectomy in myeloid leukemia is practically always fatal, whereas splenectomy in Banti's disease, done early, is absolutely curative. The blood examination easily differentiates between the two diseases.

Differential Diagnosis.—Other diseases to be ruled out in making a diagnosis of Banti's disease, besides these just mentioned, are (1) aleukemic lymphadenosis, (2) lymphosarcoma of the spleen, (3) splenomegaly due to tuberculosis, and (4) the other forms of splenomegaly described in this section.

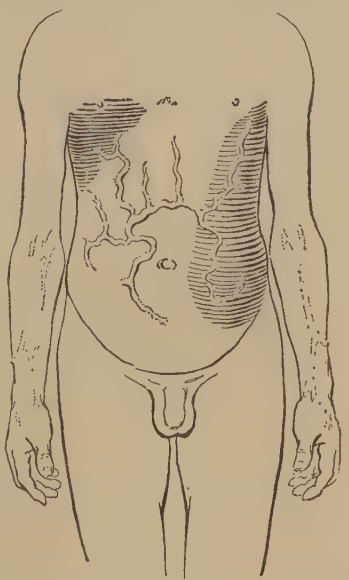

Fig. 321.—Diagram Illustrating Atrophic Liver with Splenomegaly (Banti's Disease). Note the Small Liver, the Large Spleen, and the Signs of Collateral Circulation and of Ascites.

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ix. Splenomegaly of the Gaucher Type

This condition is often described as a sub-variety of Banti's disease, but it probably differs entirely from it pathogenetically. It is characterized clinically by chronic splenomegaly, enlargement of the liver, moderate anemia, and a peculiar brownish or grayish discoloration of the skin, occurring in families. The disease is very rare.

The blood shows no constant alterations, though there is usually a marked anemia, with signs of regeneration on the part of the bone-marrow (normoblasts, and sometimes megaloblasts), and of irritation of the leukopoietic tissue of the bone-marrow (a few myelocytes in the blood). In some cases there is leukopenia.

The splenic enlargement is due to accumulations of very large cells (up to 40 μ in diameter), resembling endothelial cells. Similar groups of cells are found in the liver, in the bone-marrow, and in the lymph glands, so that in all probability, we have to deal here with a peculiar systemic tissue-disease involving the whole leukopoietic apparatus, just as in the leukemias. Gaucher believed that these cells are all endothelial in origin, but later studies suggest that they are derived from the connective tissue rather than from endothelium. According to Riesl, the cells contain a peculiar protein body distantly related to hyaline, or to amyloid.

The disease is due neither to tuberculosis nor to syphilis.

Differential Diagnosis.—(1) From *Banti's disease* (no pigmentation of the skin, not hereditary, more progressive); (2) from *Addison's disease* (no splenomegaly; no enlargement of the liver).

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x. Splenomegaly in Chronic Congenital Hemolytic Jaundice

Much attention has been paid of late to a form of splenomegaly, occuring in families, in which the signs are present from birth on. It is usually referred to as "hemolytic jaundice," "hemolytic icterus" or "congenital" and "family icterus."

Congenital and Familial Hemolytic Icterus.—This condition has been studied in recent years, especially by the French writers. It occurs, however, in all countries, and American observers are beginning to report cases. My colleague, Professor Thayer, has shown me an interesting case which he has had under observation many years, and I, myself, know of an American family in which the disease was recognized several years ago; now and then, we see a case in the general clinic.

The disease is, however, rare. The principal symptom is the jaundice, with urobilinuria, urobilinogen, moderate anemia, enlargement and hardening of the spleen, and slight enlargement of the liver. The disease is hereditary, and has been traced in a number of cases through several generations. There is genuine jaundice, not simple brownish pigmentation of the skin as in the Gaucher type of splenomegaly.

Autopsies have been made in at least two cases (Minkowski, Vaquez). There is simple hypertrophy of the spleen. The large endothelial cells, so characteristic of the Gaucher type of splenomegaly, are absent.

The disease is essentially a hemolytic icterus. The osmotic resistance of the red blood-corpuscles is abnormally low. Whether or not this depends upon an imperfect blood formation (hereditarily defective erythropoiesis), or upon hemolysis of normally former corpuscles due to some unknown noxa, is not yet certain, though the former view seems more probable.

Chauffard has recently called attention to the relationship of hereditary lues, and of tuberculosis, to hemolytic jaundice. In one family, the fifty-year-old father and his two daughters had been jaundiced and anemic from birth. The resistance of the R. B. C. varied from 0.64-0.62 NaCl—a very high value for the minimal resistance. The Wassermann reaction was positive.

Chauffard treated a number of cases with salvarsan and was astonished to find a further reduction in the resistance of the red cells as well as an increase in the jaundice, and of the hemolysins in the blood.

On applying tuberculin tests, a number of cases of congenital hemolytic jaundice have shown sharp reactions. In one case reported by Chauffard, the spleen doubled in size, the minimal resistance of the R. B. C. changed from 0.64 to 0.76, and erythroblasts and red cells showing basophilic granulations appeared in numbers in the circulating blood.

The disease should be differentiated from other splenomegalies (Banti's disease, Gaucher's type, etc.).

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Part VIII

Diagnosis of Diseases of the Digestive Apparatus

Section I

METHODS OF EXAMINATION

The digestive apparatus includes (A) the *cavities of the mouth and pharynx,* and the *digestive tube proper.* The latter consists of (B) the *esophagus,* (C) the *stomach,* (D) the *small* and the *large intestines* and the *rectum,* (E) the *pancreas,* and (F) the *liver.* On account of its close association with these organs, the methods of studying (G) the *peritoneum* will here also be discussed.

A. Examination of the Mouth and Pharynx

1. The Lips, and the Mucous Membrane of the Mouth

On *inspection* of the mouth cavity one can make use of a spatula of metal, of wood, or of glass. "Wooden tongue blades" can be purchased in boxes, eight dozen in a box. A wooden blade, once used, can be destroyed, which simplifies dealing with infectious and malignant cases. With the blade, the mucous membrane of the cheek can be separated from the molar teeth, and the tongue can be depressed. If daylight be good, no reflector is necessary. At other times, a reflecting mirror or an electric headlight may be used for illumination. On inspecting the pharynx, the patient is asked to say "ah," to raise the palatine curtain. The spatula should not be permitted to touch the base of the tongue, otherwise the gagging reflex will be elicited.

Should a young child refuse to open its mouth, the nose may be held for a few moments to enforce mouth-breathing; a spatula can then be introduced between the teeth and the mandible further depressed. During crying, a brief view may often be obtained.

Palpation with the finger may be necessary to determine the consistence of a

mass on the tongue or tonsil, or when feeling for adenoid vegetations in the nasopharynx. The finger should be covered with a sterile finger-cot of very thin rubber.

On the lips, and on the buccal mucous membrane, we pay attention to the following points:

(a) *Color* (pallor, cyanosis, inflammatory redness); (b) *swellings;* (c) *mouth breathing* (adenoid vegetations; idiocy; dyspnea); (d) *cracks, fissures,* or *rhagades* (sores at the angle of the mouth, especially in children with congenital lues); (e) *"cold sores,"* or *water blisters* (herpes labialis); (f) *luetic lesions* (primary sore, or chancre, on lip, tongue, or tonsil; mucous patches of secondary syphilis; ulcers or gummata of tertiary syphilis, often on the fauces); (g) *epithelioma* of the lip; (h) *angioneurotic edema* (sudden, painless swellings without apparent cause; history of similar swellings there or elsewhere); (i) *thick lips* (myxedema; acromegaly; (j) *hare-lip* (often associated with cleft palate); (k) *Koplik's spots* (in measles, *q. v.*); (l) *leukoplakias* (irregular circumscribed whitish or gray areas); and (m) *pigmentations* (brown or black areas of pigmentation occurring in Addison's disease; similar areas may be seen in normal negroes).

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2. The Breath

Foul breath (*fetor ex ore*) is most often due to (a) negligence in brushing the teeth or cleaning the tongue, (b) decomposing plugs in the tonsils, (c) ozena or antrum disease, (d) stomatitis, (e) fetid bronchitis, (f) decomposing food in an esophageal diverticulum, (g) fermentative dyspepsia, and (h) gases given out through the lungs, owing to absorption from the intestines in some cases of coprostasis.

A **fruity odor** to the breath, resembling the odor of over-ripe apples, may be associated with acidosis connected with deficient carbohydrate

metabolism (diabetes; vomiting; fever; starvation). The urine should be tested for the presence of diacetic acid and acetone.

A **urinous odor** to the breath, resembling the odor of trimethylamin, is observed in uremia. A peculiar carrionlike odor may be present in agonal states.

The **alcoholic breath** may be very deceptive; the odor differs with different intoxicants (whisky, beer, champagne). A patient of mine, who was taking seven pints of champagne each day surreptitiously, was noticed by her husband to have a peculiar odor to the breath that he thought was due to some drug, rather than to wine.

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3. Saliva and the Salivary Glands

The saliva is a mixture of the secretion of the parotid, submaxillary and lingual glands and of the mucous and serous glands of the lips, cheeks, tongue and palate. It is normally alkaline, but may become acid in certain diseases (diabetes, cancer of the stomach, pernicious anemia, etc.). It contains in addition to mucin and inorganic salts, a small amount of potassium sulphocyanide and a diastatic ferment (ptyalin). Of the formed elements normally present may be mentioned, (1) leukocytes, (2) squamous epithelium, (3) bacteria and fungi. The normal total salivary excretion amounts to 1,000 or 1,500 c.c. daily.

The *functions* of saliva are (1) to moisten foods and to lubricate them for swallowing, (2) to dissolve gustatory substances, and (3) to begin the digestion of starch.

Salivary Disorders.—The saliva may be *pathologically increased* (SALIVATION; PTYALISM) in mercurial poisoning, in pilocarpin therapy, in pregnancy, in diseases of the pancreas, and in certain nervous diseases.

The saliva may be *pathologically diminished* (OLIGOSIALIA) in the diseases in which the body loses much water (fever, diabetes, cholera, contracted kidney, etc.). It results in dryness of the mouth and difficulty in speaking and chewing. The dryness of the mouth after the administration of belladonna or atropin should always be kept in mind; it may follow the use of belladonna suppositories for hemorrhoids. Very rarely patients are seen in whom a gradually increasing diminution of salivary secretion occurs, leading eventually to almost complete suppression (XEROSTOMIA). The cause of the condition is unknown.

Changes in the Salivary Glands.—A salivary gland may be *enlarged* in inflammations (*e. g.*, mumps), or in tumors. All the salivary glands, along with the lacrimal glands, may be simultaneously enlarged (**Miku-**

licz's disease). Stone is sometimes palpable in a salivary duct (*sialolithiasis*). A retention cyst in the salivary duct is known as a *ranula.*

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4. The Teeth and Gums

There are 20 *milk teeth:* on each side of each jaw there are five of these deciduous teeth (two incisor teeth, one canine tooth and two molar teeth). The physician should try to keep in mind the times at which they normally appear.

There are 32 *permanent teeth,* 8 on each side of each jaw: 2 incisor teeth, 1 canine tooth, 2 premolar teeth (bicuspids), and 3 molar teeth. The first molar tooth is the first permanent tooth to break through. It comes in the fourth or fifth year of life, behind the posterior molar milk tooth. In the seventh year, the middle incisors follow, those of the upper jaw coming before those in the lower. In the ninth or the tenth year, the anterior premolar appears; in the tenth to the eleventh year the canine; in the eleventh to the twelfth year, the second premolar. The second or middle premolar appears between the twelfth and the thirteenth year, while the third molar (wisdom tooth) breaks through between the sixteenth and the thirtieth year, or it may not come through at all.

On examining the teeth we pay attention to (1) the completeness of the set, (2) the arrangement in the jaw, and (3) peculiarities about individual teeth.

Delayed dentition is often seen in families that suffer from rickets or from abnormalities of the thyroid (goiter; myxedema; etc.). When the first dentition is delayed, the sequence of appearance of the teeth may be altered. The permanent teeth in such persons are often badly developed, misshapen, or eroded. Dentists who specialize in *orthodontia* can do much to "straighten" teeth when they appear in abnormal positions. This is very important for a proper occlusion, for the development of the jaw bones and the shape of the face, and for the prevention of oral sepsis in later life. Children manifesting heterodontia should be taken early to an orthodontia specialist.

Caries of the teeth (erosion; cavity formation) should be carefully

watched for; the loss of a tooth is always a serious matter. Dental caries can lead also to digestive disturbances. Sudden and extensive caries should excite the suspicion of diabetes and lead to a careful testing of the urine for sugar.

The *teeth in hereditary syphilis* are often deformed. The two median incisors in the upper jaw show a concave notch at the cutting edge (**Hutchinson's teeth**), and some of the other teeth may be small and peg-shaped. An illustration of these Hutchinsonian teeth has been given in Part IV.

In prolonged jaundice in childhood, *green teeth* may be seen (Thursfield). In chronic tetany, *parallel transverse dark-colored stripes* may be seen on the teeth, due to defect in the enamel. In the status lymphaticus cases, it is not uncommon to find the two *central incisors abnormally large* and the two lateral incisors very small.

The **gums** should always be closely examined. *Spongy, swollen, bleeding gums* may indicate scurvy, some other form of hemorrhagic diathesis, or mercurialism. In chronic lead poisoning, a grayish black line (*lead line*), due to the deposit of lead sulphid in the papillae, can be been in the gum, close to the teeth. It cannot be wiped off, nor does the blue color disappear on pressure. On microscopic examination, the dark granules are found to be in the connective tissue of the papillae.

Suppuration between the gums and the teeth, leading to loosening of the teeth, is known as **pyorrhea alveolaris** or *Riggs' disease*. A piece of paper drawn between the teeth and saturated with the pus yields a characteristic sickening sweetish odor. Microscopic examination of the pus may reveal the entameba buccalis, spirochaetes, and bacteria. The great importance of pyorrhea alveolaris as a portal of entry in metastatic infections (*e. g.*, arthritis; endocarditis; nephritis), and as a source of general intoxication (sapremia) should be kept in mind.

A nodule appearing on the gum may be an **epulis** (osteosarcoma).

An abscess at the root of a tooth, causing swelling of the gum and face, is familiarly known as a *gum-boil* or *alveolar abscess*. Dead teeth and especially crowned teeth are often the site of *blind abscess*, or *periapical abscess*. This may not show externally, and it is well, in cases of arthritis, endocarditis or grave anemia to have *film röntgenograms* made of such teeth.

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[Note.—See also references under Special Diseases of the Teeth.]

5. The Tongue

Protrusion of the Tongue.—Normally, a patient when asked to show his tongue does so promptly, and protrudes it in the middle line. Should it deviate to one side, tests should be made to see if unilateral paralysis exists (*e. g.*, in hemiplegia). It may be tremulous (alcoholism; fever; dementia paralytica), and in dementia paralytica it is often protruded with great suddenness. After a few moments of protrusion, patients usually withdraw the tongue, but dull patients may leave it out until ordered to take it in again. In cases of progressive bulbar paralysis fibrillary twitching is often best seen in the tongue.

If a patient does not show the tongue on request, it may be (1) because he is deaf, or (2) because, though he hears, he does not understand the words (sensory aphasia), or (3) it may be due to negativism (as in dementia praecox).

Shape and Size of the Tongue.—*Swelling* of the tongue is often indicated, not only by its size, but by indentations at the margins due to the teeth (*anemia*). A very *large tongue* may be seen in myxedema or in acromegaly. *Unilateral atrophy* or *bilateral atrophy* of the tongue may be due to bulbar paralysis or to lesions of the hypoglossal nerve (*q. v.*).

Color and Moisture of the Tongue.—The tongue may be abnormally *bluish* (cyanosis), *pale* (anemia), or unusually *red* (diabetes; strawberry tongue of scarlet fever). It may be unusually *moist* (salivation), or abnormally *dry* (fever, etc.), in which event it is often *rough, fissured,* and, sometimes, covered with crusts (*sordes*).

Coating of the Tongue.—This is of very little help in diagnosis. Those that smoke or drink, and often others, apparently healthy, have

coated tongues, especially in the morning. Persons that do not masticate thoroughly, and those on milk diet, always have coated tongues. If the teeth be markedly defective on one side, the tongue will be coated on that side, as mastication will be performed almost wholly with the other side. In persons whose tongues are usually clean, a coated tongue may follow constipation, fever, or dyspeptic disturbances.

An *abnormally clean tongue* is often met with in gastric hyperacidity, in ulcer of the stomach, and, occasionally, in pernicious anemia with anacidity.

In *typhoid fever,* the coating usually leaves the tip and the lateral margins free, and there may be a peculiar mouselike odor to the breath.

A dark brown or blackish color on the back of a tongue otherwise thickly coated is sometimes spoken of as black-hair tongue (*nigrities linguae*); it is due to pigmentation of elongated, hyperplastic filiform papillae. A yeastlike organism (*Cryptococcus linguae pilosae*) has been described as the cause of black tongue.

The *geographical tongue,* not infrequent in children, is characterized by the appearance of round, or serpiginous, areas of desquamated epithelium. The cause is unknown. It should not be confused with *syphilitic plaques* of secondary lues. The latter are rounded, or irregular-shaped, whitish areas.

Nodules and Ulcers of the Tongue.—Nodules may consist of chancres, gummata, tumors (carcinoma) or blastomycotic nodules. Tuberculous and syphilitic ulcers sometimes appear. No simple ulcers of the mouth should be neglected (danger of cancer if not quickly healed). When the nature of a nodule or an ulcer is not clear, a portion should be excised for histological examination or animal inoculation.

Herpes of the Tongue.—Herpes linguae or "canker" of the tongue appears as minute, painful vesicles, which quickly rupture, leaving minute grayish ulcers with a hyperemic periphery. These heal quickly, especially if touched with caustic ($AgNO_3$; HNO_3).

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6. The Fauces and Pharynx

In the **fauces,** or **throat,** we inspect the *palatine curtain* (velum), the *uvula* and the *palatine arches* (glossopalatine arch; pharyngopalatine arch). Between them, we examine the *palatine tonsil,* with its crypts

or fossulae. We test the movements of the soft palate and the palatal reflex.

In *paralysis of the soft palate* (*e. g.*, in postdiphtheritic neuritis) liquids swallowed come back through the nose. Unilateral paralysis can be detected by inspecting the velum when the patient says "ah," for one side of the palate will remain immobile.

The **pharynx** is divisible into three parts: (1) nasal, (2) oral, and (3) laryngeal. The nasal part (nasopharynx) can be inspected by anterior or posterior rhinoscopy (*q. v.*), or palpated by the sterile index finger. Very satisfactory views can be obtained by any one of the several electrical pharyngoscopes now on the market (Hays; Holmes; Schmuckert). The two most important structures to be examined here are, (1) the *pharyngeal tonsil*, hypertrophy of which gives rise to so-called adenoid vegetations, and (2) the *orifice of the eustachian tube*.

Waldeyer's Ring of Lymphatic Tissue. This is composed of (1) the pharyngeal tonsil, (2) the lingual tonsils, and (3) the two palatine tonsils. Scattered nodules of adenoid tissue occur also in the pharyngeal recess (fossa of Rosenmüller) and in the posterior wall of the pharynx.

This lymphatic ring of Waldeyer may be hyperplastic in its whole extent, so that not only adenoid vegetations but hypertrophy of the palatine tonsils and enlargement of the lingual tonsils exists. This condition is often seen in scrofulous children and in the so-called **exudative diathesis** of Czerny. Enlargement of the lingual tonsils should always be palpated for, when status **thymicolymphaticus** is suspected in adults.

Adenoid vegetations may make nasal breathing impossible. The patients are mouth-breathers, have a stupid facial expression, snore at night, have a nasal twang (on saying "good-morning"), and are subject to nasal catarrh, bronchitis, and recurring attacks of otitis media. A chain of glands is usually palpable down the back of the neck on one or both sides.

In **hypertrophy of the palatine tonsils** respiration may also be interfered with, leading to a marked *Harrison's groove* in the chest.

Inflammations of the throat and tonsils (anginas) are recognized by the presence of redness, swelling, and of exudate.

Luetic ulcers, scars and gummata are common in the tonsils, palatine arches, and in the soft and hard palate. Luetic perforation of the palate is a characteristic finding.

The pharyngeal reflex (*gag-reflex*) is altered in vagotonic states (*q. v.*).

Retropharyngeal abscess, causing the posterior wall of the pharynx to project forward, and yielding fluctuation on palpation, should not be overlooked.

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B. Examination of the Esophagus

1. Introduction

The **esophagus**, or **gullet**, averages 25 cm. in length, in adults, measured from its beginning in the pharynx behind the cricoid cartilage in front of the sixth cervical vertebra, to its opening at the cardia of the stomach at the level of the 10th or 11th thoracic vertebra. The approximate distance from the incisor teeth to the uvula is 7 cm., to the entrance to the esophagus opposite the cricoid 15 cm., to the bifurcation of the trachea 25 or 26 cm. and to the cardia 39 or 40 cm. The esophagus is divisible into three parts: (1) cervical, 5 cm., (2) thoracic, 18 cm., and (3) abdominal (subphrenic), 2-3 cm. Clinically, its relations, in its upper part to the trachea; at the level of the bifurcation of the trachea to the left bronchus, the bronchial glands, the pleura, the pericardium and the recurrent laryngeal nerves; and lower down, below the bifurcation, to the aorta, are very important. The diameters of the lumen increases on the average from above downward, varying from 7 to 22 mm. Normally, certain *constrictions* occur at different levels. Three of the most important are: (1) at the beginning of the cervical portion (behind the cricoid cartilage), (2) behind the bifurcation of the trachea at the level where the aorta crosses the esophagus, and (3) where the esophagus passes through the diaphragm (hiatus esophageus). Pieces of bone and other foreign bodies are apt to be arrested at such physiological narrowings. The upper one can be reached by operative procedures; the lower one can be dilated.

On swallowing corrosive fluids, or when there is injury on passing esophageal

bougies, the damage occurs most often at the level of one of these normal constrictions; thus scars are more common in these situations, and cancers also tend to develop in the same regions.

Deglutition is a complex reflex, which may be initiated voluntarily, but is in largest part independent of the will. When studying disturbances of deglutition, the student should refresh his memory of the normal physiology. Most careful studies were made early by Kronecker and Meltzer. Recently, with the aid of x-rays, deglutition has become better understood (Cannon, F. Kraus). Cinematography shows that two periods can be distinguished (1) a buccopharyngeal and (2) an esophageal. The former lasts less than 1½ seconds, the latter 4 to 7 seconds. The two periods have been compared to the atrial and the ventricular activity of the heart.

In the anamnesis, difficulty in swallowing (dysphagia), pain on swallowing, a localized feeling of pressure in the course of the tube, or regurgitation of food, makes an examination of the esophagus necessary. *Dysphagia* may set in suddenly or may begin insidiously and gradually increase. In esophageal stenosis, especially, the patients state that they have been compelled to use foods of ever softer consistency until, finally, only fluids could be swallowed. They either regurgitate food immediately, or they feel that it remains in the esophagus to be regurgitated later on, perhaps in a decomposed, foul-smelling state. Such patients emaciate rapidly.

Where there is great variation in the ability to swallow, a *cardiospasm*, or a *diverticulum* of the esophagus, may be suspected. Pain on swallowing may be sharply localized (*ulcer; carcinoma*), or may be diffuse throughout the whole length of the gullet (*esophagitis*).

Regurgitation of food (esophageal vomiting) is characterized by the absence of hydrochloric acid; the reaction is usually alkaline and the "vomitus" contains large quantities of mucus.

Only the upper part of the esophagus is accessible to direct inspection. Palpation and percussion are useful only in the cervical portion (diverticula). The auscultation of the "deglutition murmurs" is not very important in diagnosis.

If one listen near the xiphoid cartilage, after a patient has swallowed a mouthful of water, two murmurs may be audible (Meltzer); a primary, so-called *squirting,* murmur, and soon after, a secondary, so-called *squeezing,* murmur. Usually, only one of these murmurs is present in the same person, though, in exceptional cases, both murmurs may be audible. Meltzer regards a distinct squirting after a single act of swallowing as evidence of insufficiency of the cardia; a total absence of squeezing murmurs may indicate stenosis of the cardia.

The three important methods of examining the esophagus are: (1) the passage of esophageal bougies, (2) x-ray examinations of the esophagus, and (3) esophagoscopy. Of these three methods, the second, is probably that from which we obtain most help.

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2. The Passage of Esophageal Bougies

Contra-indications.—Before passing a sound, or a bougie, through the esophagus to clear up the nature of a difficulty in swallowing, the heart and large vessels should be carefully examined, and if an aneurism be found or even be suspected to exist, no bougie should be passed. Fatal hemorrhage has more than once occurred from rupture of an aneurism by an esophageal bougie.

Other contra-indications are outspoken circulatory insufficiency, recent vomiting of blood, acute mediastinitis, and severe cachexias.

In no instance should strong force be used in passing a bougie, for if there be an ulcer, or if the wall of the gullet be thinned by an abscess in the neighborhood, perforation may easily occur.

Instruments.—It is best to begin by passing an ordinary soft stomach tube in the usual way (*q. v.*). Only if this meets with resistance at any point is recourse to a firmer instrument (sound, bougie) necessary.

For sounding the esophagus, the whalebone sounds with olive-shaped tips, or mushroom-shaped tips, of varying size are most often used. Gum-elastic bougies are also employed. Recently, the use of a silk thread previously swallowed as a guide to the sound has proven very useful (Plummer, Sippy); in cases in which the stricture is tight, or the channel through it tortuous, the silk thread is not alone sufficiently strong to hold the tip of the bougie safely in the path, and it is wiser therefore in such cases first to pass a piano wire, which by means of a small guide-ring at its end is strung on the silk thread. When the tip of the wire is in the stomach, bougie tips of suitable size may be threaded on the external end of the wire and passed down the esophagus: the stiff wire guides them safely through the lumen of the stricture.

The sound is lubricated with a little glycerin or with vaselin. Old sounds are to be avoided if at all rough, as they easily injure the mucous membrane.

Technic.—The patient sits on a stool, the body bent slightly forward and the head a little backward, a basin in one hand (in case of vomiting). He is told to hold the mouth wide open, to breathe quietly and regularly, and to avoid gagging. He should be assured that the examination is harmless and painless. The physician stands in front of, or on one side of, the patient. With the curved forefinger of his left hand he makes strong

pressure downward and forward upon the tongue, thus drawing the epiglottis and the cricoid forward and widening the opening of the esophagus. The bougie, held like a pen in the right hand, is now passed straight backward in the middle line to the pharynx; the upper end of the bougie is then elevated, and the sound gently slid into the esophagus. Care must be taken to avoid (1) the sinus pyriformis on each side, (2) entrance of the sound into the larynx (dyspnea, cough). Once in the esophagus, the bougie is slowly passed downward until it either reaches the stomach or

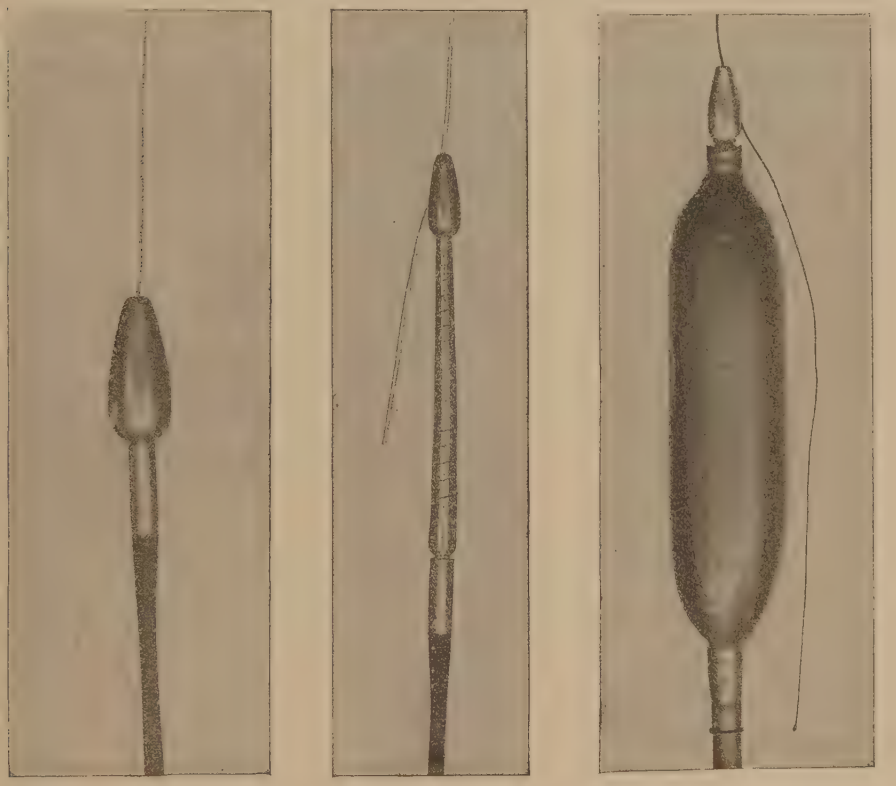

Fig. 322.—Instruments for Examination and Treatment of Cardiospasm: (a) Whalebone Staff with Olive Drilled for Silk Thread; (b) Whalebone Staff Spiral Tip and Olive; (c) Dilator. (After H. S. Plummer, Collected Papers by the Staff of St. Mary's Hospital, Mayo Clinic, published by W. B. Saunders Co., Phila.)

meets with resistance. Occasionally, a resistance is encountered that is due to temporary spasm of the wall of the esophagus. When this occurs, one waits a few moments until the spasm passes off and then proceeds with the further passage of the bougie.

When a resistance is met with, its exact position, degree, and nature should be investigated. First, its *distance from the incisor teeth* is meas-

ured, and the measurement repeated on different days to see if the resistance is constantly at the same level. The *caliber* of a narrowed esophagus is measured by finding the sound (beginning with the largest and using successively a series of smaller ones) that just passes through without the exertion of any considerable force. The *length of the narrowing* is found by passing an olive-tipped sound through to the stomach and again withdrawing it, noting the distance from the incisor teeth at which the resistance is first felt on withdrawal. The difference of the distances of the two resistances from the incisor teeth indicates the length of the narrowed portion of the tube.

The mushroom-shaped tips of Callmann permit of a careful palpation of the stenosed area; through feeling nodules or grooves in the diseased area, helpful information can be gathered that may throw light upon the *nature* of a stenosis, or obstruction.

The tips of some sounds (Bruning's) are provided at their lower end with "windows," having a sharp margin; if one of these be drawn through a stenosed area, and be rotated as it passes, a little of the surface may be shaved off, and the material thus obtained can be examined microscopically.

Causes of Stenosis.—Among the more important causes of esophageal stenosis are (1) *cicatrices* (from swallowing corrosive liquids), (2) *foreign bodies* (like false teeth or a peach stone) that have been swallowed (obturation stenosis) and (3) *neoplasm* (most often, cancer). Obstruction may be due also to (4) *spasm* of the wall of the esophagus, or of the cardiac orifice (cardiospasm), (5) *compression* of the esophagus from without (aneurism; mediastinal tumor; enlarged glands; caries of the spine), or (6) a *diverticulum* of the esophagus.

Plummer's Method of Examining Diverticula and Stenoses.—If a diverticulum be suspected, the patient is told to swallow three yards of buttonhole silk-twist with the aid of much water at bedtime, and next morning to swallow three additional yards (continuous with the first thread swallowed). The swallowing process may be facilitated by balling up the first foot of thread and placing the ball in a capsule that can be gulped down with a bite of bread; thus the thread is carried down and more can then be fed into the mouth from the spool, which it is convenient to attach by a large safety-pin to the patients' nightgown. If there be any passage through to the stomach, the thread will not only enter that organ but will also reach the intestinal canal and will have been carried to such a distance that it will bear considerable traction without being withdrawn. The outer end of the thread is now passed through a canal in the olive-tip of a whalebone instrument; it enters at the apex of the olive and passes out at its side at the other end. The sound is now introduced into the esophagus, and passed along the thread, which serves as a guide, the thread being held loosely until an obstruction is reached. If now the thread be tightened, the tip will not change its level if the obstruction

be due to a stricture; but if there be a diverticulum, the bulb of the probe will be lifted to the level of the opening into the lower esophagus, and the amount of elevation will indicate the depth of the pocket to the bottom of which the probe has first descended. The procedure is well illustrated in the figures that accompany Plummer's article.

By means of the thread, the piano wire, and a series of superimposed spindles (or olives) of graded size, strictures of the esophagus, or of the cardia, can often be satisfactorily dilated (Plummer; Sippy; Lerché).

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[Discussion], 944–949.

3. Röntgenology of the Esophagus

The diagnosis of esophageal diseases has been revolutionized since the introduction of x-ray methods. A soft tube filled with mercury, or shot, can be passed into the esophagus, or, still better, the patient may be asked to swallow bismuth porridge, bismuth mucilage, or bismuth milk, after which he is studied with the fluoroscope or by means of the x-ray plate. Oblique ventrodorsal illumination is used, the x-ray tube being placed in front on the right, and the fluoroscopic screen, or the photographic plate on the left, behind. The bismuth-filled esophagus, or the opaque tube inside the esophagus, then appears as a shadow running parallel to the spine, though separating somewhat from it below. If the stomach be previously distended with CO_2, a mercury tube passing into it can be plainly seen.

No peristaltic waves are visible on röntgenoscopy, though pulsatory movements in the lower part, due to propagation from the right atrium, may sometimes be seen.

Foreign bodies, tumors of the esophagus, mediastinal tumors causing compression, esophageal dilatations and diverticula, and esophageal stenoses

are easily demonstrable by the x-ray method (See Special Diagnosis of Diseases of the Esophagus).

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4. Esophagoscopy

A valuable but difficult method of examining the esophagus is by inspection through the esophagoscope under electric illumination. Esophagoscopy is feasible through the fact that it is possible to bring the mouth-opening, the entrance to the esophagus and the cardia into a straight line —a fact long illustrated by sword-swallowers.

Various esophagoscopes have been devised. Among the best are (1) M. Einhorn's esophagoscope with electric lamp within the tube, (2) Chevalier Jackson's instrument (combined bronchoscope, esophagoscope and gastroscope), (3) Gottstein's instrument with Caspar's panelectroscope for illumination, and (4) Bruning's esophagobronchoscope.

Technic.—For the technic of esophagoscopy, the special monographs bearing upon the subject should be consulted. The descriptions given by Chevalier Jackson of Pittsburgh are excellent. The method is not one often used except by a few that have trained themselves to become especially expert in the technic; it does not seem necessary, therefore, fully to describe it here. The following brief comment will suffice.

The pharynx of the fasting patient is cocainized, as well as the base of the tongue, the hard and soft palates, the epiglottis and the whole area around the entrance to the esophagus. The examination may be made with the patient sitting, or, better, in the recumbent position on a very high table, so that his head can be at the level of the examiner's eyes, the head, squarely extended at the atlanto-occipital joint, being properly supported and held in place by an assistant. Instead of a mouth-gag, Boyce's bite-block, or so-called thimble-gag, is used. The tube, lubricated with glycerin or butter, is introduced into the mouth and is guided by the examiner's left finger along the posterior pharyngeal wall as far as the arytenoid cartilages; the patient is then told to swallow, whereupon the instrument is gently pressed toward the esophageal entrance and usually by means of gentle rotary movements can be made to glide downward. Jackson recommends avoiding the middle line, on account of the cricoid cartilage; he inserts the tube first into the right pyriform sinus, and thence into the esophagus. Once the esophagus has been entered, the instrument usually passes smoothly onward to the cardia.

When the cardia has been reached, or an obstruction has been met with, the

obturator is removed and the illuminating apparatus adjusted. The esophagus is inspected as the tube is gradually withdrawn.

A cervical kyphosis may make esophagoscopy impossible.

Esophagoscopic View.—The esophagus in its cervical portion, viewed through the instrument, appears as a closed tube with a small slit in the middle. In the thoracic portion, it appears as an open canal (negative pressure within the thorax), with pale, red, moist mucous membrane.

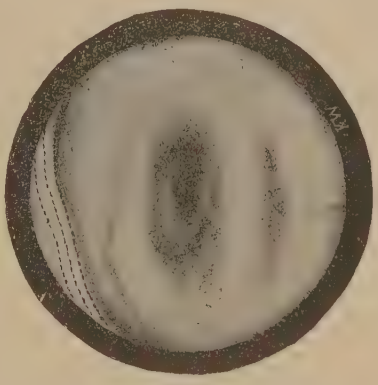

Fig. 323.—Normal Aspect of the Esophagus. Bulging of the Left Wall Due to the Beating of the Aorta. (After Quisez, in Arch. des Maladies du Cœur, published by Baillière, Tindall & Cox, Paris.)

Pulsatory, respiratory and peristaltic movements in the walls are observable. Pathological changes in the mucous membrane, or foreign bodies in the lumen, can be clearly seen (inflammations, ulcers, foreign bodies, motor disturbances such as spasms or atony, scars and stenoses, neoplasms, diverticula, etc.) (See Special Diagnosis).

The esophagoscope is useful for diagnosis but still more so for therapy (removal of foreign bodies; applications to ulcers; etc.). An open safety pin, impacted in the esophagus, can be closed and removed through the esophagoscope (Lerché).

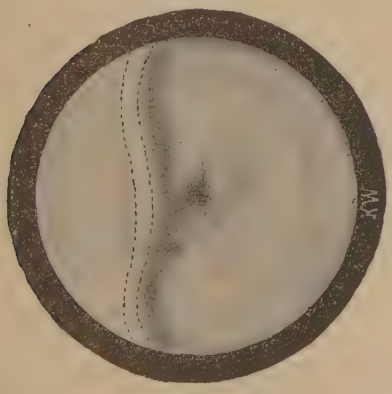

Fig. 324.—Incomplete Stenosis of the Esophagus in a Patient with Severe Spasm. (After Quisez, in Arch. des Maladies du Cœur, published by Baillière, Tindall & Cox, Paris.)

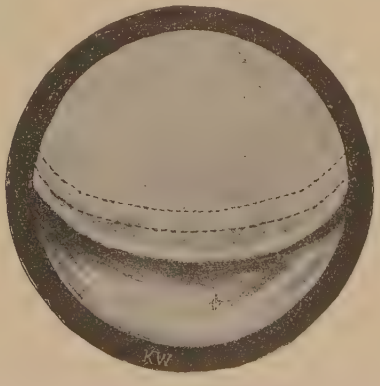

Fig. 325.—Stenosis of the Esophagus by an Aneurism of the Arch of the Aorta. (After Quisez, in Arch. des Maladies du Cœur, published by Baillière, Tindall & Cox, Paris.)

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C. Examination of the Abdomen and of the Abdominal Organs

This part of the examination will be considered under two headings: (1) general examination of the abdomen; (2) special examination of the abdominal organs.

1. General Examination of the Abdomen

(*a*) *Topography of the Abdomen*

For convenience, the abdomen is divided into *three zones* (epigastric, mesogastric and hypogastric), and *nine regions* (3 upper, in the epigastric zone, 3 middle, in the mesogastric zone, and 3 lower, in the hypogastric zone).

If we bound the abdomen proper by the diaphragm above and by the pelvic inlet below, and draw, on the anterior abdominal wall, two horizontal lines, of which the upper one passes through the point where the clavicular line strikes the costal margin on each side and connects with the corresponding point on the other side, and the lower one unites the highest point of the iliac crest on one side with the corresponding point on the other side, and then draw two oblique lines from the point where the clavicular line cuts the costal margin on each side to the tuberculum pubis on the same side, we shall have divided the abdomen into three zones and the nine regions as shown in the following table:

I. Epigastric Zone (*Zone epigastrica*).

(1) Right hypochondriac region (*Regio hypochondriaca dextra*).

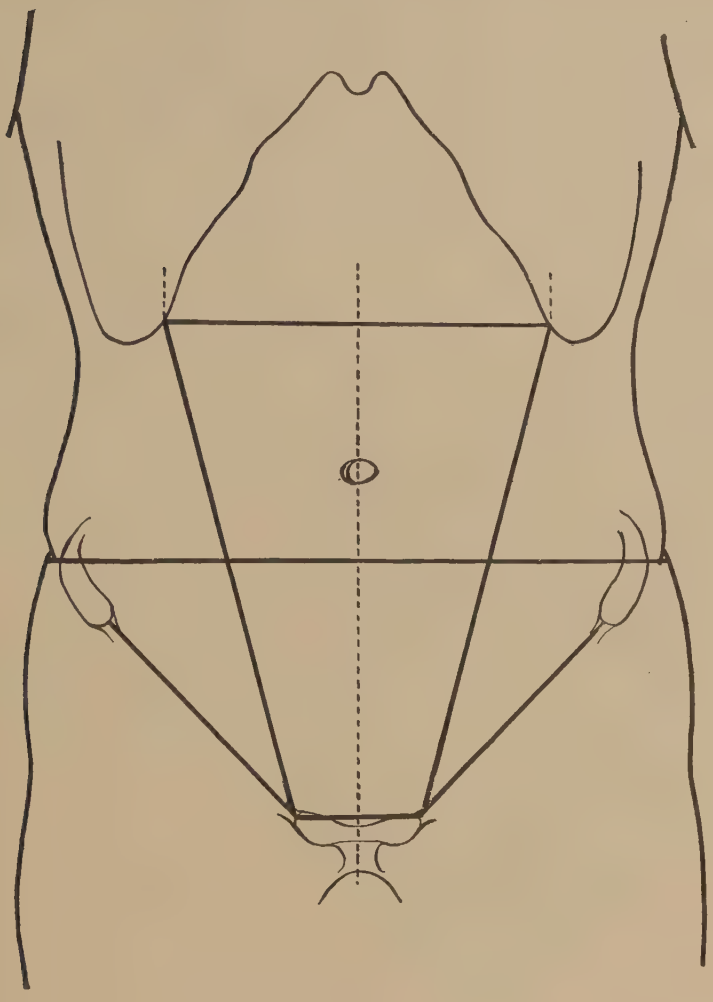

Fig. 326.—Regions of the Abdomen.

(2) Epigastric region (*Regio epigastrica*).
(3) Left hypochondriac region (*Regio hypochondriaca sinistra*).

II. Mesogastric Zone (*Zona mesogastrica*).
(1) Right lateral abdominal region (*Regio abdominis lateralis dextra*).
(2) Umbilical region (*Regio umbilicalis*).
(3) Left lateral abdominal region (*Regio abdominis lateralis sinistra*).

III. Hypogastric Zone (*Zona hypogastrica*).

(1) Right inguinal (*Regio inguinalis dextra*).
(2) Pubic region (*Regio pubica*).
(3) Left inguinal region (*Regio inguinalis sinistra*)

These zones and regions are illustrated in Fig. 327.

Post mortem studies and röntgenographic examinations have recently made clearer the relation of organs and parts of organs to these various regions. An epitome of the results of these studies is given in the following table:

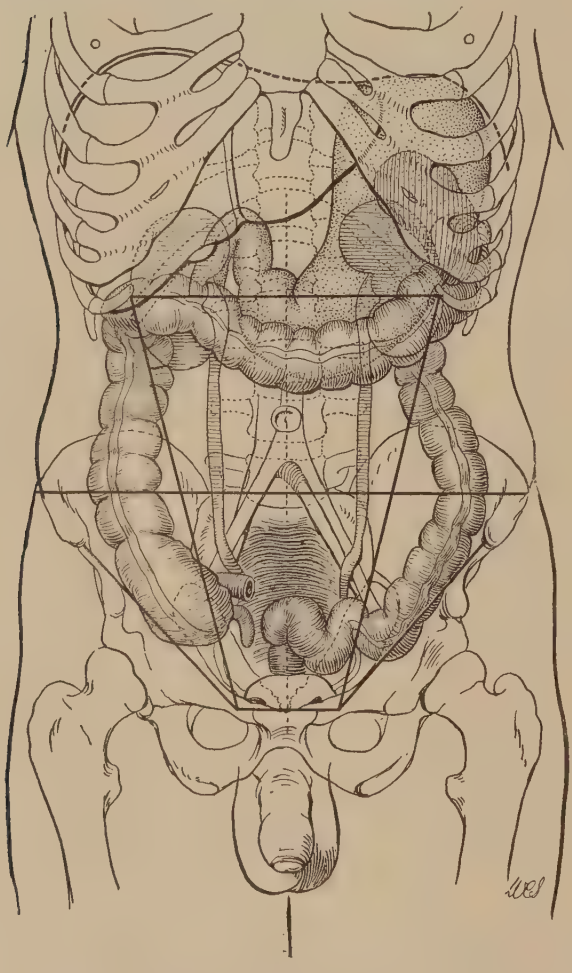

Fig. 327.—Diagram of the Position of the Several Abdominal Viscera As Regards the Regions of the Abdomen.

Right Hypochondriac Region.—Liver (most of right lobe); colon (hepatic flexure); right adrenal (lateral part); right kidney (upper lateral part).

Epigastric Region.—Liver (small part of right lobe, most of left lobe); gall-bladder; stomach (part of body and pylorus); lesser omentum; duodenum (pars superior and upper part of pars descendens); adrenal (medial part); kidney (medial part of upper half); aorta and inferior cava; celiac axis; celiac plexus; thoracic spine.

Left Hypochondriac Region.—Liver (small part of left lobe); stomach (fundus and part of body); spleen; colon (splenic flexure); tail of the pancreas; lateral part of left adrenal; upper lateral part of left kidney.

Right Lateral Region.—Ascending colon, covered usually with loops of small intestine; lateral part of lower half of right kidney.

Umbilical Region.—Most of small intestine, covered by greater omentum; stomach (part of body and of pyloric end); mesentery; transverse colon; duodenum (second portion of pars descendens; pars inferior); head and body of pancreas; medial part of lower half of kidneys, with pelvis of kidneys and upper

part of abdominal portion of ureter; retroperitoneal lymph glands; aorta and inferior cava with their large branches; lumbar spine.

Left Lateral Region.—Descending colon, usually covered with loops of small intestine; left kidney (lateral part of lower half).

Right Inguinal Region.—Cecum with vermiform appendix and lower end of ileum; iliac fossa; iliopsoas muscle.

Pubic Region.—Part of small intestine; urinary bladder (when distended); end of sigmoid and beginning of rectum; ureters; sacral promontory.

Left Inguinal Region.—Sigmoid; iliac fossa; iliopsoas muscle.

In the general examination of the abdomen we use the methods of inspection, palpation, percussion and auscultation. Of these, by far the most important are inspection and palpation. Palpation is the most important of all, but may be found difficult in some patients owing to thickness of the abdominal wall or to muscle spasm. The patient should lie upon a firm, narrow bed, at least three feet high and in a good light, the source of light being preferably at the foot of the bed.

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(*b*) *Inspection of the Abdomen*

On inspection, we pay attention to, (1) the surface of the abdominal wall, (2) the general contour of the abdomen (distension; retraction), (3) the presence of visible patterns and of visible movements, (4) localized projections and depressions, and (5) any evidence of visceroptosis.

i. The Surface of the Abdominal Wall

Cutaneous *eruptions* are looked for, especially in febrile cases for the rose spots of typhoid fever. Abnormal *pigmentations* are sometimes marked on the abdominal wall (Addison's disease; chronic tuberculosis). Lineae albicantes, or *white striae*, following various conditions that stretch the skin (obesity, pregnancy, cysts, tumors, etc.) are to be noted. *Scars* of previous wounds or incisions may throw light upon the case.

Especial attention should be paid to the condition of the *subcutaneous veins* of the abdomen. In cirrhosis of the liver, the central veins may be markedly distended through the formation of a collateral circulation (*caput medusae*); in obstruction of the inferior vena cava, it is the lateral veins

of the abdomen, especially the thoraco-epigastric veins, that become dilated as the collateral circulation is formed.

ii. General Contour of the Abdomen. (Distention; Retraction)

Among the causes of **abnormal distension** of the abdomen are:

1. **Fat.**—This may be deposited in the abdominal walls themselves, in the preperitoneal tissue, and in the mesentery, especially in general obesity. The fat may be laid down diffusely or in more localized masses. The latter are sometimes painful, especially in adiposis dolorosa (Dercum's disease). I have seen two cases in which epigastric pain was due to such painful fat in the mesentery, confirmed by laparotomy. It is sometimes difficult to distinguish between painful fat nodules and the pain of hernia of the linea alba, cholelithiasis, gastric ulcer, appendiceal epigastralgia or spastic colitis.

2. **Edema.**—This might at first be taken for fat, but the presence of general anasarca, the predominance of the edema in the lateral and dependent portions of the abdomen, and, especially the pitting on pressure with the finger, serve to distinguish.

3. **Meteorism, or Gaseous Distension of the Intestine.**—The navel is not retracted, and the percussion note is markedly tympanitic in contrast with the fatty or edematous abdominal wall, in which the note is dull. Generalized meteorism with elevation of the diaphragm and diminution of liver dullness is to be distinguished from local forms of meteorism due to collection of gas above an intestinal obstruction (ileus).

4. **Free Gas in the Peritoneal Cavity.**—In perforation of the stomach or intestine there is uniform distension of the abdomen. There is no visible peristalsis, since the abdominal wall is separated from the stomach and intestines by gas. The liver dullness disappears.

5. **Free Fluid in the Peritoneal Cavity (Ascites; Peritoneal Exudates).**—The abdomen is uniformly distended, though, in the recumbent position, the abdomen broadens, owing to the collection of fluid in the flanks ("frog's belly"). In the upright position, the abdomen protrudes markedly and the navel projects outward. Percussion (revealing movable dullness) and palpation (yielding a "fluctuation wave") are decisive, though they are not demonstrable until the fluid exceeds a certain amount.

6. **Large Cysts, Ovarian Tumors, or Advanced Pregnancy.**—Large pancreatic, hydronephrotic or ovarian cysts may cause general distension simulating ascites, but the percussion relations are different, since, in ascites, the note is always tympanitic at the highest part of the abdomen, owing to the fact that the light intestines swim upon the fluid. Advanced pregnancy could scarcely be overlooked on careful examination.

Among the causes of **abnormal retraction** of the abdomen may be mentioned:

1. **Cachexia,** especially after inanition from any cause (*e. g.*, esophageal stenosis, pyloric stenosis, anorexia nervosa, carcinoma).

2. **Spasm of the wall of the abdomen** and of the intestines (*e. g.*, in tuberculous meningitis, and in lead poisoning). In such instances boat-shaped retraction is seen—the so-called "scaphoid abdomen."

iii. Patterns and Visible Movements

In emaciated persons a **pattern,** due to the coils of the intestines, may be visible through the thin abdominal walls. In intestinal obstruction, the "*patterns of abdominal tumidity*" (John Wyllie), may be of great value in diagnosis. Thus, in obstruction of the lower end of the large bowel, the horseshoe-shaped colon may stand out prominently, and even the sacs or haustra of the colon may be visible. In obstruction at the cecum, or at the lower end of the ileum, the pattern is in the lower umbilical region; during spasm, the coils of the small intestine may stand out prominently, parallel to one another, as oblique or transverse bands—the so-called "ladder pattern." In obstruction at the duodenojejunal junction (gastromesenteric ileus), there may be only slight distention of the upper part of the abdomen; here, vomiting is usually a marked feature, with symptoms of severe general intoxication.

Fig. 328.—Patient with a Pyloric Tumor, Causing Stenosis with Dilatation of the Stomach. Note the Prominence of the Epigastrium and the Medulatory Waves of Peristalsis. The Crosses are Placed on the Three Prominent Waves. The Letter *f* Indicates the Depression on the Lesser Curvature. (After Hewatson in W. Osler's "Lectures on the Diagnosis of Abdominal Tumors.")

Of the **movements** sometimes visible on inspection may be mentioned: (a) respiratory, (b) pulsatory, and (c) peristaltic movements. The **respiratory**

movements of the abdominal wall may be limited, or may cease altogether, in peritonitis, in lead-colic, or in diaphragmatic pleurisy; they may also be limited when the diaphragm is pushed up by fluid or gas in the peritoneal cavity, or by large cysts or tumors. The respiratory mobility of masses in the abdomen may be helpful in the differential diagnosis of abdominal tumors (*q. v.*).

Pulsatory movements in the abdomen are often wrongly interpreted. A moderate grade of epigastric pulsation, due to the abdominal aorta, or to transmitted pulsation from the right ventricle, can usually be seen. In nervous women, in anemia, and in Basedow's disease, the throbbing due to this cause may be marked, and I have often seen patients in whom a mistaken diagnosis of abdominal aneurism was made on account of this pulsation. The pulsation in aneurism is forcible and expansile, and, usually, on palpation, a definite tumor can be felt, while a systolic murmur is audible on auscultation. Tumors of viscera in front of the aorta may yield a pulsation transmitted from the aorta. Pulsation of the liver may be visible, and palpable, in tricuspid insufficiency and, occasionally, in aortic insufficiency.

Visible **peristaltic movements** are of great importance in diagnosis. Thus, visible gastric peristalsis usually indicates pyloric stenosis. The slow contraction wave can be seen to pass from left to right across the epigastrium as the patient lies on his back in a tangential light. When pyloric stenosis is suspected, we may try to excite visible peristalsis by rubbing the surface of the abdomen with ice, or by slapping it with a towel wrung out of cold water. In intestinal obstruction, visible peristalsis may be seen proximal to the obstruction and be helpful in localizing it.

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iv. Local Projections and Depressions

Local projections may be due to the enlargement of individual organs, to hernias, to tumor formation or to abscess. Local depressions are rare.

v. Evidences of Visceroptosis or Splanchnoptosis

Inspection may give the first clue to the existence of visceroptosis. In the **acquired form of visceroptosis,** due to relaxation of the abdominal walls and of the mesentery, seen so often in thin women after multiple pregnancies, there is usually marked *diastasis of the recti muscles;* if we ask the patient (in the recumbent position) to raise her head, marked

bulging appears between the recti. Such a patient, on standing, may show a markedly pendulous abdomen due to the atrophy and flaccidity of the abdominal walls. Often, the whole hand can be introduced between the recti muscles, and the individual organs can be grasped.

In the **constitutional form of visceroptosis,** the shape of the thorax and abdomen are characteristic (*habitus enteroptoticus, asthenia universalis*). Such patients have a long flat thorax (*thorax paralyticus*) with narrow epigastric angle, fluctuating tenth rib, and lumbar lordosis. On standing, the abdomen projects, though the abdominal walls, in contrast with the acquired form, may be rigid. The viscera are found on palpation and percussion to occupy a lower position than normal. Visceroptotic patients are often neurasthenic, especially when under weight; they have labile vasomotors, and atony of the stomach and intestines.

The so-called **splanchnoptotic index** (Becher-Lennhoff) is obtained as follows: One divides the distance of the jugulum from the upper margin of the symphysis by the minimal circumference of the abdomen, and multiplies the result by 100:

$$\text{Index} = \frac{\text{jugulo-pubic distance}}{\text{minimal abdominal circumference}} \times 100$$

On the average, the index in normal women in the recumbent position is 75; in the standing position, a little less. In man, it is less than 75. A higher index (over 80) is met with in people with palpable kidneys and asthenic habitus.

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(*c*) *Palpation of the Abdomen*

This is the most useful method in abdominal diagnosis, but to attain skill in its use, long practice is required.

i. Technic of Abdominal Palpation

The patient lies flat on his back, without pillow, is told to relax the abdomen, and to breathe quietly and deeply with his mouth open. It will sometimes help if he also flex the thighs. In obscure cases, it is desirable to repeat the palpation on various occasions. When the intes-

tine is distended by gas or feces, it should be first emptied by giving an enema. When ascites exists, palpation may not be very instructive until after paracentesis has been performed. In a few cases, when the abdomen is held rigid, it may be necessary to make the examination in a warm bath, or under anesthesia.

The physician should be seated comfortably beside the patient and should proceed leisurely, making sure that the palpating hand is always kept in a comfortable position.

The palpation should be, first, superficial and, later, deep. On **superficial palpation,** the hand should be laid flat upon the abdomen, with slight pressure, to accustom the patient's muscles to contact. Later, this pressure may be gently and gradually increased. The hand should be kept flat, the fingers not flexed; by palpating with a broad surface we avoid causing pain and muscular contractions. One palpates, first, the abdomen as a whole, and, afterwards, methodically investigates the several regions, comparing, especially, symmetrical regions of the abdomen with one another. Regions known to be painful should be avoided at first, and should be approached only after the non-painful areas have been examined.

After the patient has become accustomed to superficial palpation, the **deeper palpation** may be undertaken. Here the finger tips may be used, the fingers being held perpendicular to the long axis, or to the margin, of the structure to be palpated. The physician's nails should be kept short. It is desirable that the palpating fingers be relaxed; to meet this condition, on deep palpation one may reinforce the palpating fingers by pressure from the other hand, the latter directing the movements and the former following passively and devoting itself exclusively to the perception of the palpatory peculiarities; "the left hand guides, while the right observes."

On deep palpation, one should attempt, in the middle line, to palpate the spine and the sacral promontory, and, lateralward, the iliac fossa and the iliopsoas muscle. On investigating the hypochondriac regions, the patient is told to breathe deeply. Bimanual palpation with the fingers of one hand in the costovertebral angle, making contra-pressure from behind, is also especially useful in investigating the hypochondriac regions and the lateral abdominal regions. On palpating the spleen, one pulls forward the lower thorax with left hand and palpates with the right hand.

In palpating the two inguinal regions, it is occasionally helpful to have the patient extend his leg and raise his foot eighteen inches from the bed; the contracting iliopsoas muscles then approaches the anterior abdominal wall. Bimanual palpation, with one hand examining through the rectum or vagina, may also be useful.

Occasionally, help may be gained by palpating with the patient lying on his face in the knee-elbow position, or when he is standing.

Dipping, or making a short thrust with the palpating fingers into the depth, is used to excite a fluctuation wave in ascites, and, sometimes, to reach an organ, or tumor, situated beneath fluid (*e. g.*, the edge of the liver in ascites).

Deep palpation is, sometimes, extremely difficult, or may even be impossible, on account of (1) *obesity*, which can be overcome largely by the so-called "hydrostatic examination" in the warm bath; (2) *excessive distension* of the abdominal walls by gases or fluids in the digestive tube, in the urinary bladder or in the peritoneal cavity—to be overcome by emptying these as far as possible; or (3) *muscle spasm*, especially of the recti, to be overcome by patience, and by diverting the attention of a nervous patient by conversation or by deep breathing; examination in the warm bath or after hot linseed poultices may be necessary or, in rare instances, under anesthesia.

ii. Results of Palpation of the Abdomen

We gain information, by palpation, especially regarding the following points: (1) the state of the abdominal wall; (2) the size, form, position and consistence of the abdominal organs; (3) abdominal pain or tenderness; and (4) abdominal tumors and resistances.

State of the Abdominal Walls.—Here, palpation extends the information gained by inspection regarding (1) deposits of fat and (2) edema. Painful areas, tension of the walls, and defensive muscular spasm in inflammatory processes involving the peritoneum, are discovered.

Size, Form, Position and Consistence of the Abdominal Organs.—Each organ is palpated separately, first by *gliding palpation* (the palpating fingers moving over the organ, or its edge, perpendicular to its long axis). In some instances, the axis of the hand may be held obliquely to the axis of the structure palpated, using the index and middle finger, or the middle finger, ring finger and little finger as palpators ("oblique two-finger palpation," or "oblique three-finger palpation," of Hausmann). In some cases, the ulnar or radial margin of the hand may be used in this gliding palpation ("marginal palpation" of Hausmann). Gliding palpation is especially valuable in the examination of the stomach and intestines.

After examination by gliding palpation, each organ may be examined by deep palpation, in which the organ is fixed by the fingers, in contrast with gliding palpation, in which they slide over its surface. The palpation of single organs is described further on.

Palpation in Abdominal Pain or Tenderness.—*Pain* in the abdomen may be spontaneous, or it may occur only on palpation. The exact *localization* of either kind of pain may be very important in diagnosis. The exact *character* of a pain in the abdomen is always important. The pain of colic is a typical instance. In this, the pain sets in suddenly,

gradually increases in intensity to a maximum, and then, usually, slowly decreases again. Such "colicky pains" are usually due to spasmodic contraction of structures containing smooth muscle (gall-bladder or urinary bladder around a stone, ureters, pylorus, intestine, etc.).

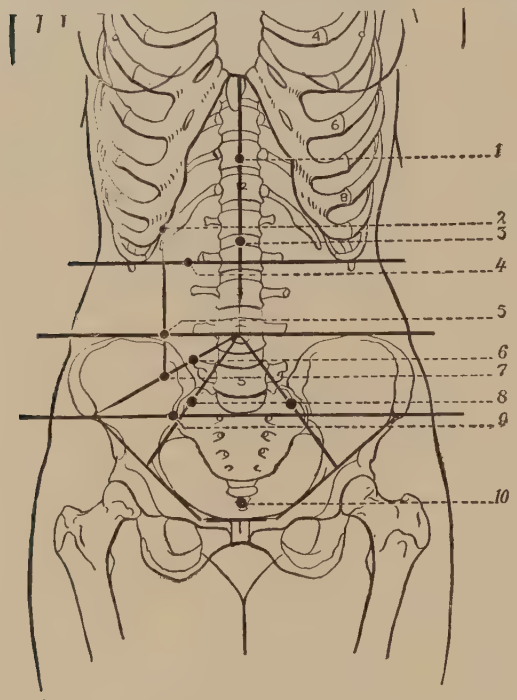

Fig. 329.—Abdominal Pain-points. 1. Epigastric Point; 2. Gall-bladder Point; 3. Gastric Point; 4. Solar Point; 5. Para-umbilical Point; 6. Morris' Point (Appendicitis); 7. McBurney's Point (Appendicitis); 8. Lanz's Point (Appendicitis); 9. Ovarian Point; 10. Uterine Point.

The *time of appearance* of a pain and the *relation* of this *to food intake* may be of great importance in the diagnosis of gastric and duodenal affections, especially ulcer (*q. v.*).

By *tenesmus* is meant a painful spasm of the sphincter ani and neighboring muscles, along with intense and rapidly recurring desire for stool, with violent straining; there is burning pain in the rectum and anus, and usually only small amounts of feces are evacuated. It points to affections of the rectum or colon.

On palpation, one may discover either a *diffuse tenderness* or a *circumscribed painful area;* the former is often associated with intestinal catarrh; the latter most often points to local, or circumscribed, peritoneal irritation. A local pain on palpation in the linea alba, between the navel and the xiphoid, may indicate a hernia of the linea alba or a gastric ulcer; pain on palpation in the region of the gall-bladder may point to cholecystitis or gall-stones; pain on pressure in the region of McBurney's point or below it, to appendicitis.

Segmental cutaneous hyperesthesia (Head's zones) may be looked for in cases of abdominal pain (see Part XII).

Palpation of Abdominal Tumors and Resistances.—On the discovery of an *abnormal mass* in the abdomen, it should be carefully palpated to establish its exact position, size, shape and consistence, its mobility on external pressure, on respiration, and on distension of the stomach or intestine with air, its sensitiveness to pressure, and its relation to neighboring organs.

Certain appearances, not due to real tumors, simulate abdominal tumors, and the examiner should be on his guard against them. These

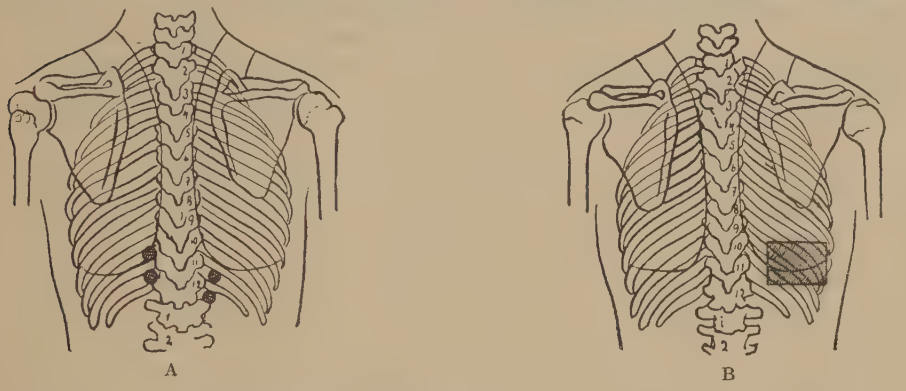

Fig. 330.—(A) Dorsal Pressure-points in Gastric Ulcer; (B) Dorsal Pressure-zone in Cholelithiasis. (After H. Elsner, in Lehrb. d. Magenkrankheiten, published by S. Karger, Berlin.)

are (1) the so-called *sham tumors*, in which normal structures, in certain states, awaken the idea that a pathological state exists; and (2) *phantom tumors* or masses that are a direct expression of pathological functional states.

Sham Tumors

A so-called "sham tumor" may consist of a mass of fat, an area of abdominal muscle in contraction, a loop of intestine, or a portion of another normal organ.

The three principal sham tumors met with, however, are (1) a palpable aorta, (2) a palpable pylorus, and (3) fecal masses.

Palpable Aorta.—In patients with thin retracted abdominal walls and an empty gastro-intestinal tract, it may be possible easily to palpate a pulsating aorta, and the patient may complain of pain in the region of the aorta and of troublesome throbbing there (*aortismus abdominalis, phantom aneurism, student's aneurism!*).

Palpable Pylorus.—Normally, the pylorus is not accessible to palpation, as it is covered by the liver, but in pyloroptosis, or when the liver is small, or displaced upward, the pylorus may become palpable, especially in emaciated patients (*e. g.*, in pulmonary tuberculosis). In such cases, it may be felt as a horizontal, or oblique cord, the size of the index finger or thumb, passing from a point from 2 to 7 cm. above the navel obliquely upward and to the right just beneath the right M. rectus. Sometimes, instead of a cord, a round tough nodule, the size of a hazelnut, beneath the right rectus muscle, and 1 or 2 cm. above the level of the navel, may be felt. The most characteristic feature of both cord and nodule is the

frequent, rapid, change in its consistence; when palpated for a few seconds, the formation of the cylinder or nodule can be distinctly felt. Its consistence rapidly increases until it may reach that of cartilage, after which it may again relax suddenly, with a palpable (and, sometimes, audible) squirt, and then cease to be palpable altogether. The squirt can be felt to pass from the left toward the right (Cohnheim), whereas similar squirts in the transverse colon pass in the opposite direction.

Fecal Masses.—Retained fecal masses (scybala) often simulate tumors, and have been known to deceive the very elect. Such masses are most often situated in the cecum or the sigmoid; in other words, in one iliac fossa. More rarely, they lie in the transverse, or the descending, colon. Occasionally, such a mass is felt just beyond the hepatic flexure in the right hypochondrium, where it may simulate a kidney.

Such masses are usually superficial; they are, as a rule, spherical or cylindrical in shape, though, in some instances, they are wholly irregular in outline. The surface, though sometimes smooth, is usually nodular and uneven. The consistence varies, but is usually characteristically doughy; pressure with the finger leaves a dent, as though in putty. When demonstrable, this peculiar doughy consistence, or plasticity, is pathognomonic. Now and then, a fecal tumor possesses stonelike resistance. It should be kept in mind that a fecal mass may lie proximal to a true neoplastic mass.

In rare instances, if the finger be pressed slowly into a fecal mass so that the intestinal mucous membrane sticks to it, and one then gradually withdraws the finger, it may be possible to perceive the loosening of the mucous membrane from the feces ("sticky symptom," or so-called "Gersung's phenomenon"). Fecal tumors can usually be removed by purgation or by enema, though, especially where a diverticulum exists, this may be very difficult. Such fecal tumors are usually associated with chronic constipation. In a few cases, they are accompanied by diarrhea, in which event the fecal mass lies in a diverticulum, or, if it lie in the lumen, it is canalized.

X-ray examination is helpful in the diagnosis of these cases of chronic constipation with fecal impaction.

Phantom Tumors

These have long puzzled clinicians. They occur usually in hysterical or very nervous persons; they are more frequent in women than in men, and in youth than in advanced life. They may appear without apparent lesion anywhere. A remarkable feature is that they may suddenly change in size, shape and position after having been constant for weeks or months. They always disappear under anesthesia, but may suddenly reappear on the return of consciousness.

Among such tumors may be mentioned, (1) circumscribed muscular

contraction of the anterior abdominal wall, including the so-called phantom appendix (Treves); (2) a displaced liver; (3) pylorospasm and enterospasm; and (4) the so-called tympanitic abdominal tumor. The latter may be either circumscribed (false pregnancy) or diffuse (false peritonitis).

True Abdominal Tumors

On using palpation to determine the location of an abdominal tumor, one first determines its topographical site (as regards the various regions in the abdomen), then ascertains its continuity, or discontinuity, with neighboring organs or masses, its relation to the stomach and intestine, and its mobility (respiratory, manual, postural, peristaltic, etc.).

A decision can often be made regarding the situation of a tumor by ascertaining its periphery when the stomach or colon are distended with air or CO_2. In this connection, the following table may be helpful:

iii. Differential Diagnosis of the Location of Abdominal Tumors (After Boas).

Tumors	On Blowing up Stomach	On Blowing up Colon
1. Of the Stomach:		
(*a*) Pylorus	Moved toward the right and downward; feel broader and less sharply limited.	All moved upward.
(*b*) Anterior abdominal wall and greater curvature		
(*c*) Lesser curvature	Vanish completely.	
2. Of the liver	Moved upward and to the right, the anterior margin of the organ becoming more distinctly palpable.	The lower margin of the mass is moved upward; a tumor of the gall-bladder will be shoved forward. In very large tumors, there may be no change of position.
3. Of the spleen	Moved toward the left, and, often, also downward.	Moved upward and to the left. Movable tumors become demonstrable now in the region normally occupied by the spleen.
4. Of the large intestine	Moved downward.	Not moved upward.
5. Of the kidneys		Moved at first somewhat upward, and, finally, vanish in the depth. A movable kidney returns to the normal kidney region. In large neoplasms of the kidney, only the medial margin becomes indistinct.
6. Of the great omentum	Moved downward	Moved downward.
7. Of the pancreas	Vanish.	

Of the points that can be utilized for making a diagnosis of the *character of a tumor* may be mentioned: (1) its shape and size; (2) its surface; (3) its consistence; (4) the percussion note over it; (5) pulsations and bruits; (6) tenderness or pain; (7) exploratory puncture or laparotomy.

Displaced or so-called **dystopic organs** (kidneys, spleen, liver, cecum) may be mistaken for tumors. Diseases of the organs other than neoplasms may also simulate tumors (See Special Diagnosis).

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(*d*) *Percussion of the Abdomen*

The patient is placed in the recumbent position and the abdominal walls relaxed. As a control, it may be desirable also to percuss in the lateral position, or in the knee-elbow position. Certain organs (pancreas, ovaries, uterus) are normally not accessible to percussion. The solid organs, like the liver, spleen and the distended urinary bladder, can normally be delimited by light percussion ("no-sound stroke") from gas-containing parts (stomach; intestines).

The separation of gastric tympany from intestinal tympany is sometimes difficult, though usually the former is somewhat higher pitched than the latter. To make the contrast greater, one may distend either the stomach or the colon with air or CO_2 and then percuss (See Percus-

sion of the Stomach). Intestinal tympany may be abnormally great or it may be replaced by dullness.

When *the tympany over the abdomen is abnormally great,* it may be due either to distension of the intestine with gas **(meteorism; tympanites)** or to the presence of free gas in the peritoneal cavity (perforation of the stomach or intestine). In the latter case, the tympany will be most marked at the highest levels of the abdomen and will change with change of position; more important still, the liver dullness diminishes or disappears. If free fluid also be present in the peritoneal cavity, the dull note due to it will have a horizontal level with tympany above it, just as in hydropneumothorax.

Abnormal dullness in the abdomen may be due to (1) fecal accumulation; (2) superficial tumors; (3) inflammatory exudates (appendicitis; tuberculous peritonitis; etc.); (4) cysts of the ovary, pancreas or kidney; (5) thick abdominal wall from obesity or edema; or (6) empty intestine in emaciation.

(*e*) *Auscultation of the Abdomen*

This is only rarely of help in diagnosis. The normal peristaltic movements of the intestines may cause gurgling. When loud, this gurgling may be audible at a distance (*borborygmi*). In nervous persons, a lively peristalsis of the intestine may cause loud rumbling and splashing of its contents (*tormina intestinorum*).

Occasionally, in peritonitis (local or general), *peritoneal friction* gives rise to a leathery sound (*bruit de cuir,* or "Bright's murmur"), which may also be palpable. This may be heard during respiratory movements or during peristaltic movements. It is due to fresh exudate, and not, as Bright thought, to peritoneal adhesions. It is, perhaps, heard most often over the liver in acute perihepatitis.

The bruit audible over an *abdominal aneurism* has already been referred to.

In cases of incomplete obstruction of the small intestine due to peritoneal adhesions, tremors, etc., the passage of intestinal contents by the obstruction is usually attended by colicky pain. If at the onset of such a pain the stethoscope be applied to the abdominal wall over the site of the obstruction, loud rumbling noises will be heard that culminate in a squirting sound. At the same instant the patient experiences relief from the pain. The squirting sound of fluid forced by the point of stenosis is very characteristic.

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(*f*) *X-Ray Examinations of the Abdomen*

Recently much use has been made of the x-ray in the diagnosis of gastric and intestinal disorders, particularly as a method of studying the form, position and motility. The mode of application will be taken up in connection with the study of the several abdominal organs.

(*g*) *Exploratory Laparotomy*

In certain *acute cases*, serious symptoms (violent pain, collapse, leukocytosis) may point to a grave lesion in the abdominal cavity, the nature of which cannot, by medical means, be certainly determined. In such instances of urgency, it is advisable to resort immediately to exploratory laparotomy. In certain obscure *chronic cases* of intra-abdominal affections, also, where the symptoms make it probable that a lesion of the gall-bladder, of the pylorus, of the duodenum, or of the appendix exists, and yet only a probable, not a certain, diagnosis can be made by medical methods, the state of affairs may be explained to the patient and exploratory laparotomy advised.

2. Special Examination of the Several Abdominal Organs

We have now to consider the special methods of examining (1) the stomach; (2) the intestine; (3) the pancreas; (4) the liver, and (5) the peritoneum. The methods of examining the kidneys and the pelvic organs will be dealt with in other sections of this book.

D. Special Examination of the Stomach and its Functions

1. Normal Anatomy and Physiology of the Stomach

Since the development of x-ray examinations and the introduction of the physiological-experimental methods of Pawlow, great strides have been made in increasing our knowledge of the normal anatomy and physiology of the stomach.

(*a*) *Form and Position of the Normal Stomach*

The stomach as a rule stands vertically in the left side of the abdomen; only one-sixth of the stomach (pyloric end) lies in the right half of the body.

The stomach varies in form normally in different people, corresponding to variations in the course of the lesser curvature, which usually passes from the

cardia at first a little to the left, and then almost vertically downward, to turn finally to the right to the pyloric end.

On x-ray examination of the stomach filled with bismuth porridge, it is found that the form of the stomach is markedly influenced by the position of the body; thus, on standing, the above vertical form is most common, while in the recumbent position the fundus is higher and, the pylorus remaining fixed, the form of the stomach approaches that of a sandal.

The fundus and body (corpus) of the stomach lie chiefly in the left hypochondrium. The lesser curvature and the pylorus are normally completely covered by the liver. The greater curvature descends normally to a level 2 to 4 cm. above the umbilicus, varying of course according to the amount of stomach contents. The fundus is the highest part of the stomach, reaching a level opposite the 4th intercostal space just beneath the left side of the diaphragm. It is this portion of the stomach that is filled with gas and yields the so-called "stomach bubble" (*Magenblase*) in x-ray pictures.

The relations of the stomach to adjacent organs are often of importance clinically. Behind it, lies the pancreas and the lesser omentum (bursa omentalis). The lesser curvature lies close to the left lobe of the liver. The fundus and the greater curvature are related to the diaphragm, the spleen, the left kidney and the transverse colon. Only a small part of the stomach (lower anterior surface and greater curvature) is normally in contact with the anterior abdominal wall. A large part of the stomach corresponds, in position, to the semilunar space of Traube demonstrable on percussion over the ribs in the left lower thorax.

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(*b*) *Functions of the Normal Stomach*

We shall consider (a) gastric motility, (b) gastric secretion, and (c) absorption from the stomach.

i. Normal Gastric Motility

Two forms of motility must be distinguished from one another: (1) the tonic contraction of the circular muscle around the stomach contents (*peristole*), and (2) the slow waves of contraction that pass from left to right toward the pylorus (*peristalsis*).

From the standpoint of motility, the stomach is divisible into two functionally separate halves by an indentation at the junction of the body of the stomach (corpus) with the antrum pyloricum. At this constriction, there is a special muscle, known as the M. sphincter antri pylori. In the fundus and body of the stomach, the tonic, or peristolic, motility predominates. In the antrum pylori, the peristaltic movements predominate. The contractions of the muscles of the wall of the stomach and their relations to the feelings of hunger have been graphically studied by Carlson of Chicago.

The pylorus opens and closes reflexly, the mechanism being under the control of nerve fibers in the duodenum, which are stimulated chemically. As long as the contents of the duodenum are acid in reaction, the pylorus is kept firmly closed; water, alkali, and salt solutions cause it to open (*acid-reflex,* or *pyloric-reflex,* of Minkowski).

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ii. Normal Gastric Secretion and Gastric Digestion

The glands of the stomach secrete the gastric juice (*succus gastricus*), consisting chiefly of, (1) **hydrochloric acid** (coming from the cells of the gastric glands proper), and (2) the **zymogens** of the ferments (coming from the chief cells of these glands and from the pyloric glands).

From these zymogens, three ferments are formed: (1) *pepsin* (a proteolytic ferment), (2) *rennin* or *chymosin* (a casein-precipitating ferment), and (3) *lipase* (a fat-splitting ferment).

About 1,500 c.c. of stomach juice are normally secreted daily. The pepsin and hydrochloric acid perform a very important digestive function in that they lead to *hydrolytic cleavage of the proteins,* with formation of soluble albumoses and peptones; some proteins (*e. g.,* white fibrous tissue) must first be acted upon by the stomach juice before the trypsin of the pancreatic juice can have any effect upon them.

The **functions of the HCl** of the stomach juice are manifold, and include, (1) the interruption of the activity of the ptyalin of the saliva, (2) a bactericidal effect, (3) the activation of the zymogens to ferments, (4) the regulation of the closure of the pyloric orifice, (5) the stimulation of the production of secretin in the duodenum, which in turn, on absorption, increases the pancreatic secretion.

The *secretion of the stomach juice* is largely under the domain of the autonomic nervous system, its secretion being favored by stimulation of the N. vagus and inhibited by stimulation of the N. sympathicus.

The secretion is produced (1) under the influence of appetite (seeing, smelling or tasting foods), (2) through mastication, and (3) through the direct chemical action of certain foods upon the mucous membrane.

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iii. Absorption from the Normal Stomach

Very little is absorbed from the stomach, but the contents (*chyme*) are sent, by small rhythmical ejections, into the duodenum; water leaves most quickly, other fluids less quickly, while solid foods remain longest in the stomach. The pylorus thus exercises a kind of selection from among the constituents of the chyme. Water seems never to be absorbed from the stomach, and sugar and alcohol are absorbed only in small amounts.

Regurgitation of Intestinal Contents into the Stomach.—Under certain conditions, and especially after the ingestion of fat, the duodenal contents may be regurgitated into the stomach, so that the stomach juice is mixed with pancreatic juice and succus entericus. The quantities may be so large as to change the peptic gastric digestion into digestion of the tryptic intestinal type.

In studying the acidity of the stomach-juice, this possibility must always be kept in mind. On occasion, the fact may be turned to account in order to obtain pancreatic juice and bile for diagnostic purposes (*q. v.*).

2. Methods of Investigating Gastric Conditions

For the clinical study of the stomach we pay attention to (a) the special anamnesis, (b) the examination of the form, size and position of the stomach, (c) the motility, (d) the secretory and digestive functions, and (e) the state of the mucous membrane of the stomach as inspected through the gastroscope.

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[NOTE.—See also references under Special Diagnosis of Diseases of the Stomach.]

(*a*) *Special Anamnesis in Gastric Cases*

Here we pay particular attention to (i) certain subjective (dyspeptic) symptoms, (ii) the age and sex of the patient, (iii) the habits of the patient, (iv) the association of gastric symptoms with diseases in other parts of the body.

i. Subjective (Dyspeptic) Symptoms

Under this caption may be mentioned (1) disturbances of appetite, (2) gaseous eructations, (3) heartburn, (4) pressure, and pain, in the epigastrium, and (5) vomiting.

The *duration* of such dyspeptic symptoms may be an aid in diagnosis. In nervous diseases of the stomach (gastric neuroses), and in gastric disturbances associated with diseases in other parts of the body, the symptoms may have lasted for a very long time, often for years; while in organic disease of the stomach itself (especially in carcinoma), the patient may have had a perfectly healthy stomach until a few weeks or months preceding the consultation, when the symptoms set in acutely.

1. **Disturbances of Appetite.**—The appetite may be diminished or may be completely lost (*anorexia*). Such anorexias may be met with in the psychoneuroses (anorexia nervosa), or they may be associated with organic disease of the stomach (cancer of the stomach, chronic gastritis, dilatation of the stomach).

The appetite is sometimes pathologically increased (*bulimia; polyphagia*). This is often the case in hyperacidity and in nervous disturbances, or it may be a symptom in Graves's disease, in diabetes or in tapeworm. One young girl, a psychasthenic, whom I saw with Julius Friedenwald, rose at regular hours during the night to eat, even when she had to prepare the food herself; and on going to the theatre, she always took raw eggs with her to swallow at intervals during the performance. In such instances, great care must be taken to rule out duodenal ulcer before deciding that the condition is "neurotic."

A perverted appetite (*parorexia*) is often seen in chlorosis, in pregnancy, and in the neuroses. The patients have an abnormal craving for sour things, for chalk, for dirt, or for various indigestible foods. Sometimes there is a special distaste for certain foods (*e. g.*, meat, in cancer of the stomach).

In some patients, despite liberal eating, the appetite never seems sufficiently satisfied (*acoria*); in other cases, a patient may begin to eat with a good appetite but after a few mouthfuls becomes satiated (*hypercoria*). When a patient fears to take food, the condition is known as *sitophobia* (M. Einhorn); this symptom is often present with ulcer of the stomach.

2. **Gaseous Eructations.**—Some patients are much bothered with belching, the emitting of gas noisily from the stomach (*eructatio nervosa*).

Though this may be due to abnormal fermentative processes, it is often due to the swallowing of air (*aerophagia*); it is met with especially in neurasthenic men and hysterical women. In cholelithiasis, gaseous eructation is a common symptom; a distinguished surgeon of my acquaintance is responsible for the diagnostic aphorism: "Fat, forty, belches gas—gall-stones!"

In rare instances, during abnormal fermentation, there may be belching of H_2S gas. This is inflammable, and one man told me that, on occasions, he had set fire to it on lighting his cigar!

3. **Heartburn (cardiagia)** is the name given to a burning sensation in the esophagus, felt behind the sternum, due to the regurgitation of acid contents from the stomach. It may be due either to HCl or to organic acids.

4. **Pressure and Pain in the Epigastrium.**—It is important always to determine whether a patient has *actual pain* in the region of the stomach, or only a *feeling of pressure*. The purely functional disturbances are rarely associated with actual pain. Real pain (*epigastralgia*) usually indicates the presence of some organic disease in the stomach itself (ulcer, stenosis, carcinoma, etc.), or in an adjacent organ (gall-stones, duodenal ulcer, intestinal colic).

If a **feeling of pressure** alone be present, it is important to determine whether it is constantly there, or only after eating, and, in the latter case, whether it depends upon the quality of the food ingested or not. When constantly present, a feeling of pressure may be due to a gastric neurosis (hysteria), or to enlargement of an adjacent organ (liver, spleen). When the pressure occurs only after eating, independently of the quality of food ingested, the symptom is probably due to a gastric neurosis; but when it occurs only after eating hard foods (bread, meat, cabbage, etc.), it may indicate a chronic gastritis or an ulcer.

When real **pain** exists, its exact *character* should be ascertained, whether cramplike, cutting, boring, or burning. The exact *location*, and the *direction of the radiation*, of the pain are important, as well as the *duration* and *intensity*. We should ask whether the pain comes at a definite time after eating or not, and whether it is relieved by food, by eructation, by vomiting, by defecation, or by bicarbonate of soda.

In ulcer, there is sometimes a *painful point* on the left side of the 12th thoracic vertebra, tender on pressure. The pain in ulcer is prone to occur either at once or about an hour after eating, while pain one and a half or two hours after eating speaks for ulcer at the pylorus or, more often, in the duodenum. Hyperacidity, without ulcer, can, however, cause severe pain. Pain in the fasting stomach—"hunger-pain"—points to duodenal ulcer, to abnormal fermentations, to hypersecretion, or, sometimes, to intestinal colic (from ulcer, stenosis, hernia, lead-colic, etc.).

Among the severest gastralgias, must be included the gastric crises of

tabes, the pain of lead-colic, and that of gastroxynsis (periodic, acute, hyperchlorhydria, with supersecretion, violent pains, and vomiting).

In perigastric adhesions, the pain usually follows immediately upon eating. In duodenal ulcer, the pain may stop immediately upon the swallowing of milk or even of water (closure of pylorus; food or liquid here acts "like balm to a wound"). A similar pain due to distension of the gall-bladder may be relieved by food that opens the papilla reflexly, allowing the bile to flow into the duodenum.

5. **Vomiting.**—When vomiting has occurred, we should ascertain the time of its appearance, whether early in the morning, or only after eating. We then ask the patient a series of questions. Does the vomitus contain particles of food eaten during the previous day (stagnation), or does it consist only of mucus or thin fluid? Does vomiting occur each day, or only every few days and then in large amounts, followed by relief (dilatation of the stomach)? Do paroxysms of vomiting occur, to be followed by weeks or months of freedom therefrom (as in gall-stones, chronic appendix, gastric crises, etc.)? Is the vomiting associated with migraine (as in gastroxynsis) or with menstrual disturbances? Does the vomiting follow upon ingestion of heavy foods like cheese and cabbage (as in chronic gastritis)?

In studying the cause of vomiting in a given case, the physiology of the mechanism should be kept in mind and an attempt made to determine whether the irritation is *central* (tumor cerebri, meningitis, tabes, uremia, psychoneuroses, etc.), or *peripheral,* due to (a) irritation of the gastric mucous membrane (gastritis, intoxication), or (b) reflex irritation (peritonitis, enteritis, gallstones, nephrolithiasis, appendiceal irritation, pregnancy, etc.).

It is important to distinguish between *simple regurgitation* of food (without nausea or violent contraction of the abdominal walls)—as in idiopathic dilatation of the esophagus, and in functional insufficiency of the cardia—and *true vomiting. Rumination* or *merycismus,* analogous to chewing-the-cud in animals, is a condition in which foodstuffs, once swallowed, are voluntarily or involuntarily returned from the stomach to the mouth, sometimes to be chewed over again before being reswallowed.

The amount, appearance, and odor of the vomitus should be recorded, and it should be examined chemically and microscopically.

Examination of Vomitus

The **amount of vomitus** will depend upon the time and frequency of the vomiting. Alcoholics often vomit in the early morning (*vomitus matutinus*) small quantities of mucus and swallowed saliva. A fasting stomach may also vomit an alkaline mixture of bile and pancreatic juice. In gastric crises, after the stomach has once been emptied of food, retch-

ing movements may continue with the evacuation of only small quantities. The morning nausea and vomiting of early pregnancy are usually recognizable (amenorrhea, etc.). When vomiting does not occur until several hours after food has been taken, and the amount vomited seems to be more than that swallowed, we think of motor insufficiency of the stomach (atony, dilatation). In pyloric stenosis, patients may vomit once or twice a week, the vomitus containing foods taken several days earlier, and the quantity amounting sometimes to more than a liter.

The **appearance** of the vomitus may depend not only upon the food taken (coffee, milk, red wine, spinach, etc.), or upon drugs (iron, methylene blue), but also upon pathological admixtures (mucus in gastritis, bile in regurgitation from the intestine, feces in ileus, and blood [hematemesis] in ulcer, carcinoma, acute gastritis, cirrhosis hepatis, etc.). If blood be vomited immediately after a hemorrhage has occurred, it may be bright red, but if it remain in the stomach for any length of time before being vomited, the HCl of the stomach juice turns it to a dark red or brownish-black coffee color (*coffee-ground vomitus* of carcinoma). In the latter case, the blood corpuscles may be disintegrated, and the demonstration of blood pigment will depend upon chemical tests or spectroscopic examination (see Examination of the Feces).

Mucus is usually very abundant in the vomitus in acute catarrhal gastritis and in chronic alcoholic gastritis. When, however, very large quantities (½–1 liter) of almost pure mucus are brought up, the possibility should be carefully investigated of the case being one of cardiospasm, or of esophageal stenosis.

Pus in vomitus may be due to perforation of the stomach wall by an abscess outside it, to suppuration of the stomach wall itself, or to the swallowing of pus from above (nasal sinusitis, pyorrhea alveolaris, pharyngeal abscesses, purulent sputum).

Large *parasites* in the vomitus are sometimes seen (ascaris, oxyuris).

On **microscopic examination,** besides constituents derived from the food (muscle fibers, fat droplets, fatty-acid crystals, starch granules, vegetable cells, connective-tissue fibers, etc.), we may find epithelium, white or red blood corpuscles, *parasites,* or tumor particles.

Among the vegetable *parasites* the most important are:

(a) *Sarcinae ventriculi* with their characteristic morphology, frequent in stagnation due to benign pyloric stenosis dependent upon ulcer. (If hydrochloric acid be absent and lactic acid abundant sarcinae are absent.)

(b) *Oppler-Boas bacilli;* long, coarse rods found in large numbers in stenosis with stagnation (lactic-acid fermentation).

Tumor fragments can be discovered more often than is usually thought, and may settle a diagnosis in doubtful cases (carcinoma).

In achylia gastrica fragments of mucous membrane are often found.

The **chemical examination** of vomitus follows the same lines as that for the stomach juice obtained after a test-breakfast (*q. v.*).

6. **Other Symptoms.**—In connection with subjective symptoms referable to the stomach, one should always inquire as to the presence of constipation or diarrhea, either of which may be of gastrogenous origin; thus *diarrhea,* especially in the early morning, frequently depends upon achylia gastrica, while *spastic constipation* is frequently associated with hyperchlorhydria.

The presence of *blood in the stools* (either tarry stools or occult blood) may be important in the diagnosis of gastric disease (ulcer, carcinoma).

Rapid *loss of weight* often accompanies gastric diseases. If due to anorexia, to sitophobia, or to injudicious dietary restrictions, it may be of little diagnostic importance; otherwise, it is suggestive of malignant neoplasms, though the possibility of a benign stenosis should also be kept in mind.

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ii. The Age and Sex of the Patient

These should not be lost sight of in differential diagnosis; thus we speak roughly of the "carcinoma age" (45 and over), and the "ulcer age" (15 to 35), but there are many exceptions. Gastric catarrh may occur at any time of life. The gastric neuroses are commonest in middle life and are usually associated with other neuropathic symptoms (headache, neurasthenic or hysterical symptoms). As to sex, *women* are especially prone to visceroptosis, chronic constipation, gastric ulcer, and gall-stones; *men* are predisposed to acute and chronic gastritis, to duodenal ulcer, and to cancer of the œsophagus and of the rectum.

iii. The Habits of the Patient

Immoderation of all sorts (excesses in food, alcohol, tobacco), insufficient mastication and insalivation of the food (quick lunches, bad teeth), and insufficient bodily exercise may be important. Hotel-keepers, bartenders and traveling salesmen are often victims of alcoholism (potatorium) and develop chronic gastritis or cirrhosis of the liver. Clerks, book-

keepers, and others of sedentary habits suffer much from constipation. Hard mental work and positions imposing great responsibilities predispose to neuroses of the stomach and intestine.

iv. The Association of Gastric Symptoms with Diseases in Other Parts of the Body

The frequency of dyspeptic symptoms in pulmonary tuberculosis, chronic cardiac disease, anemia, neurasthenia, cholelithiasis and visceroptosis should never be lost sight of. The possibility of a coexisting nephritis, tabes dorsalis, lead poisoning or lues should be kept in mind. Pyorrhea alveolaris and tooth-abscesses are fertile causes of gastric catarrh. The swallowing of pus through the night from oral sepsis, or from paranasal sinusitis often causes disorders of the stomach.

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(*b*) *The Examination of the Form, Size and Position of the Stomach*

Here we depend upon inspection, palpation, percussion, and x-ray examinations, relying upon no one of them alone, but drawing conclusions from the data obtained by the four methods.

i. Inspection of the Stomach Through the Abdominal Wall

Inspection yields help in only a few cases. Thus, an *acutely dilated stomach* may be visible. There may be *abnormal retraction* in the gastric region in pyloric stenosis, in gastroptosis, and even in high-grade dilatation. *Visible peristalsis* and *antiperistalsis* usually point to pyloric obstruction with hypertrophy of the gastric musculature, in which cases the stomach is enlarged and occupies a lower level than normal. Occasionally, in very thin persons, normal peristalsis may be seen in the absence of pyloric obstruction. Hour-glass stomach can rarely be suspected from inspection of the abdominal wall.

The normal *pylorus* is never visible, being hidden behind the liver, but if there be a palpable pylorus, it may sometimes become visible if one place the fasting patient on his back with the legs drawn up and the epigastrium relaxed, and give him one or two glasses of water to drink. On watching the pyloric region one may then see a projection the size of a walnut appear on the anterior abdominal wall, which passes upward for a distance of two or three fingerbreadths, and then vanishes, the whole phenomenon lasting about fifteen seconds (P. Cohnheim).

Tumors of the stomach are sometimes visible as projections on the anterior abdominal wall. The patient should lie flat upon his back in a good light, and the behavior of the mass during respiration should be noted.

ii. Palpation of the Stomach

Palpation yields much more information than inspection. By it, we determine the presence or absence of tenderness and of pain on pressure, and whether the latter is superficial or deep. Tumors, inflammatory masses, and old adhesions in the gastric region may be accessible to palpation. The palpable pylorus has already been referred to. (See General Examination of the Abdomen).

The size of a tumor, and its passive and respiratory mobility are to be determined by palpation. Pyloric tumors, when not adherent to other organs, are easily movable by the palpating hand. Gastric tumors, as a rule, do not move during respiration, except when adherent to the liver or diaphragm. The behavior of such tumors on dilatation of the stomach, or of the intestine, by gas, has been outlined in the table on page 291.

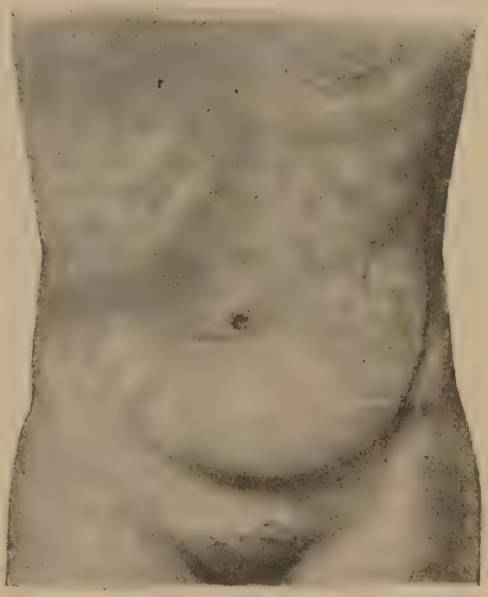

Fig. 331.—Visible Peristalsis of the Stomach in Pyloric Stenosis. (After H. Elsner, in Lehrb. d. Magenkrankheiten, published by W. S. Karger, Berlin.)

Splashing, on thrustlike palpation in the gastric region, is due to the presence of air and fluid in the stomach in certain proportions. Heard soon after a meal, or after drinking water, the sign is of no significance; but when a splashing sound can be constantly elicited, or is present as late as seven hours after the swallowing of liquid or food, it is a sign of atony, or of dilatation, of the stomach. Care must be taken not to confuse splashing in the intestine (diarrhea!) with stomach splashing.

The rule has been laid down that splashing one and a half hours after an ordinary test breakfast is a sign of deficient tonus; and that splashing two hours after a test breakfast, or six hours after a test meal, indicates not only insufficient tonus but also motor insufficiency.

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Hausmann **(*T.*).** *Ueber das Tasten normaler Magenteile. Nebst Bemerkungen zur Höhenbestimmung der Bauchorgane. Berlin,* ***1907,*** *S. Karger. 38 p. 8°.*

iii. Percussion of the Stomach

Percussion of the undistended stomach is of very little clinical value, except as regards the position of the greater curvature. It is not always easy, however, to determine the junction of stomach tympany and colon tympany, though usually the stomach yields a very low-pitched full tympanitic note, while the intestine yields a higher-pitched tympanitic note. Sometimes real help is given by auscultatory percussion, placing the bell of the stethoscope over one viscus at a time.

One of the best ways of determining the position of the greater curvature is to let the fasting patient drink two or three glasses of water and then percuss while he is standing, the water yielding a zone of dullness that disappears in the recumbent position. If one examine such a patient after each glass of water has been drunk, and determine the lower boundary of the stomach in each instance, the degree of tonus possessed by the organ can be judged of (Penzoldt-Dehio test).

Perhaps the best way to establish the position of the lower level of the stomach by percussion is to distend it first with air (pumping it in rapidly by means of a Davidson syringe attached to a stomach tube) [caution!], or with CO_2 (the patient swallowing a solution of 5 grams of tartaric acid in a half glass of water, followed by a solution of 5 grams of soda bicarbonate in a half glass of water). The patient is told to suppress any tendency to eructation. In a few moments, the position of the greater curvature will be visible on the anterior abdominal wall, or it can be exactly delimited by percussion with the handle of the hammer, or with the bowl of a spoon.

The greater curvature of the normal stomach does not descend below the level of the umbilicus on such gaseous distension; usually it remains at a considerably higher level. When the greater curvature occupies a lower level, the position is to be regarded as abnormal. If now the lesser curvature of the stomach is in its normal position, we are dealing with dilatation of the stomach, but if it be lowered as much or nearly as much from its normal position as is the greater curvature, we are dealing with gastroptosis, in which event, evidences of low position of other organs will also be found.

While this method of distension serves very well for determining the position of the stomach, it is not always satisfactory for giving us an idea as to the stomach's size, for the gas already in the stomach before distension is a variable amount, and patients lose varying amounts of gas through the pylorus or by eructation; obviously, too, the size of the stomach, as determined in this way, will vary with the pressure exercised by the CO_2 upon its walls. In pyloric insufficiency, it may be wholly impossible to distend the stomach with CO_2, or with air. From the above, it will be seen why the bismuth x-ray of the stomach gives us more satisfactory ideas of form, position and size, than does examination after distension, and, in doubtful cases, it should always be resorted to.

Some persons have congenitally large stomachs (*megalogastria*), and here gastric motility may be entirely normal. In pathological dilatation of the stomach, there is motor insufficiency (see below). A stomach of normal size may have a larger percussion area than normal, owing to (1) a small left lobe of the liver, (2) a retraction of the left lung, or (3) a high position of the diaphragm (diaphragmatic hernia); or there may be an abnormally small area of tympany (1) from enlargement of the left lobe of the liver, (2) from left-sided emphysema, pleurisy or pneumothorax, (3) from enlargement of the spleen, or (4) from dilatation of the heart.

Einhorn's Gastrodiaphany.—By the introduction of a small electric light attached to the tip of a stomach tube one can determine, in a darkened room, the size and position of the stomach through following the circle of light visible on the anterior abdominal wall as the tube is inserted and withdrawn. The method is an ingenious one, but does not yield information otherwise unobtainable, especially since x-ray methods have been employed; it has been practically abandoned.

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iv. Methods of X-ray Examination of the Stomach After Ingestion of a Contrast Meal

Great progress regarding knowledge of the form, size and position of the stomach has been made since röntgenology has been applied for the purpose. Hemmeter of Baltimore published the first report of röntgenographic examination of the human stomach in 1896. The form of bismuth "casts" of the stomach and intestines can now be studied clinically with almost as much accuracy as corrosion preparations in normal anatomy.

Two main methods have been employed—the röntgenographic method and the röntgenoscopic (or fluoroscopic) method.

(1) *Röntgenography of the Stomach*

The stomach and intestine being empty (fasting patient, after a morning stool from castor oil the night before, or after an enema), 350-400 grams of buttermilk or mashed potato, into which a suspension of 40-50 grams of chemically pure bismuth subcarbonate or, better, bismuth oxychlorid in water has been thoroughly stirred, is swallowed. Twice the quantity should be given to a very stout person. One hundred grams of barium sulphate, "chemically pure for internal use in x-ray work," *not the poisonous soluble barium sulphid*, may be used instead of bismuth, if desired, and it is now generally employed.

A coin is placed over the umbilicus and held there by adhesive. The x-ray tube is adjusted at a level about opposite the umbilicus, *i. e.*, at the 3d or 4th lumbar vertebra. The anticathode should be about 50 or 60 cm. distant from the photographic plate. It is best for the patient to stand in front of a vertical plate-holder, and the exact position should be decided upon after a preliminary röntgenoscopic view. A fairly hard tube—say 6 Benoist, or 9 Wehnelt, units—should be used, though if an intensifying screen is interposed to yield sharper contours, a hardness of 3 or 4 Benoist, or 7 Wehnelt, units may be better. In no case should a hardness of more than 8 Benoist, or 10 Wehnelt, units be used—on account of the large secondary radiation. The exposure time should be as short as possible, say $\frac{1}{3}$ to 1 second, or less, if the outfit will permit of it. The patient is told to take slow deep breaths as the examiner counts, and then to hold the breath, on command, at the end of expiration, so that, during the exposure, the diaphragm will be high and the abdomen flat.

At first bismuth subnitrate was used, but nitrite poisoning occasionally occurred; moreover, it was necessary to add milk sugar to overcome the constipating effect. Later, 50 grams of subcarbonate of bismuth (free from arsenic) came into use; with it, the danger of nitrite poisoning is averted, and, instead of a constipating, it has a slightly laxative effect. Bismuth oxychlorid, zirconium oxid (75 grams), also called contrastin, and thorium oxid (40 grams) also make satisfactory contrast materials. Barium sulphate (100 grams) is used for economic reasons, being much cheaper than bismuth carbonate, though it does not yield so intense a shadow and is therefore less satisfactory in obese patients. According to Groedel it shortens the emptying time of the stomach, the normal stomach on use of barium sulphate emptying itself within three or four hours.

A very good mixture is that of Gourevic (slightly modified):

Potato flour (or potato starch)	75.0 *g.*
Milk	1,000.0 *g.*
Almond syrup	250.0 *g.*
Barium sulphat. puriss. (sieved)	400.0 *g.*

Stir all together and pour into 2 *l.* boiling water, stir constantly. Boil for $\frac{1}{2}$ hour (or sterilize in a steam sterilizer), but do not allow more than 400 *g.* water to evaporate. While boiling, the mixture should be stirred often to prevent burning. Cool and add a concentrated formalin solution so as to make the formalin content 1:10,000. This keeps for a long time. It is of the consistence of cream and easy to drink (G. v. Bergmann).

Large plates (30 x 40 cm. or 40 x 50 cm.) should be used; the picture should include the domes of the diaphragm above and the whole rectum below.

In our x-ray department at the Johns Hopkins Hospital, Dr. F. H. Baetjer makes exposures at intervals (immediately, and after 1 hour,

2 hours, 5 hours, 12 hours, 18 hours, 24 hours, 36 hours, and 48 hours respectively); they give information not only as to position, form and size but also regarding the time required for the emptying of the stomach and for passage through the intestine. Serial röntgenography on a large scale (60-80 exposures) is of especial value, according to Cole of New York, for determining the exact form-relations in ulcer and cancer, though it is expensive to expose 60 plates for one patient (see below).

Some recommend the use of teleröntgenograms, taken at a distance of two meters, with the use of a notched string.

(2) *Röntgenoscopy of the Stomach*

Some röntgenologists prefer fluoroscopy, by means of which the changing pictures and the exact sequence of events can be followed. By means of successive röntgenoscopic views with transillumination in different directions, a composite view is obtained that they think surpasses in information that obtainable by the röntgenographic method.

This group of röntgenologists also combine röntgenoscopy with palpation of the stomach contents, thus supporting and controlling clinical palpatory findings (resistance, tenderness) by the röntgenoscopic view, and making possible the testing of the palpatory mobility of the contents of the stomach during the examination. The method has been developed especially by Holzknecht and his colleagues of the Vienna school, and, in the United States, by J. T. Case of Battle Creek, and others.

In the clinic in which I work, we have made use of both methods, röntgenography (Drs. Baetjer and Waters) and röntgenoscopy (Dr. T. R. Brown). As a rule, the results have been concordant; when discordant we make further examinations until the cause of the discrepancy is disclosed.

On röntgenoscopy the fasting patient stands before a holder to which the illuminating tube is attached, a moveable fluorescent screen hanging in front of him. After the thoracic organs have been looked at, the patient swallows a suspension of 10-20 grams of subcarbonate of bismuth or of barium sulphate in 100-150 c.c. of water. The passage of the bismuth water through the esophagus may be first observed; it may be followed through the cardia along the lesser curvature into the pars cardiaca of the stomach (recognizable by its gas bubble). The bismuth collects at first at the entrance to the pars media, where its progress is arrested by the examiner's hand held at right angles against the left rectus muscle (inspection of the pars cardiaca). After this it is allowed to flow to the deepest point of the stomach, the "caudal pole." Here, it collects in the form of a transverse crescent. By means of kneading movements made with the back of the (thoroughly protected!) left hand (the right hand holding the diaphragm and x-ray tube), the bismuth-suspension is spread out

over the caudal part of the stomach and, by effleurage movements of the back of the hand rolling against the spine, is brought into the pars pylorica, and in many cases into the duodenum. Palpation, guided by the fluorescent screen is very important for diagnosis, but the use of the hand as palpator should be given up; it is too dangerous. Its place can be taken by the mechanical "palpatorium" or "distinctor" devised by Holzknecht, or by the modification of it used by Case. A small portion of the bismuth often collects in the bulbus duodeni, or "cap"—the uppermost part of the duodenum (pars superior duodeni), the part which L. G. Cole calls the "pilleus ventriculi"; a clear space about the thickness of a lead-pencil (space of $\frac{1}{8}$ or $\frac{1}{4}$ inch) remains between the stomach shadow and the duodenal-cap shadow, corresponding to the position of the pyloric sphincter. This attempt at expression of the bismuth water into the duodenal cap must be made immediately, for the pylorus closes soon after the entrance of bismuth into the stomach. The method is useful for determining the exact position of the pylorus (not its permeability). It is possible to express it into the duodenum in only about half the cases, owing to high position of the pylorus, to tenseness of the abdominal wall, to pylorospasm, or to insufficient practice on the part of the examiner. After this attempt at expression, the peristaltic waves are examined as regards their depth and frequency, and the exact level of the caudal pole is determined. After the behavior of the bismuth water has been observed, a regular bismuth meal, say Rieder's bismuth porridge, or 350 grams of farina mush containing one part in eight by weight of barium sulphate, is next swallowed by the patient. Instead of bismuth or barium porridge, a suspension of barium sulphate in buttermilk, kephir, lozac or yoghurt is now popular. On entering the stomach, it lies on the sedimented bismuth of the watery suspension, pressing the fluid part of the latter upward; gradually, it fills the stomach. The peristaltic waves now become more marked and the course of these is carefully watched. The examiner pays especial attention to (1) the peristalsis of the antrum, and to (2) the "filling figure" of the stomach. He examines also (3) the movability of the contents of the stomach on palpation, as well as (4) the movability of the stomach as a whole, especially on retraction of the abdominal walls. Notes are made of all deviations from normal behavior. If ulcer be suspected, palpation is restricted, or avoided altogether.

The several points at which pain on pressure can be elicited in pathological states should be tested under röntgenoscopic control. Such pressure-pain points on palpation over the shadow rarely correspond to the actual location of an ulcer unless there has been perigastric or periduodenal involvement with adhesions (Case).

The röntgenoscopic view may be traced on a glass plate held before the screen. If desired, instantaneous x-ray photographs may be taken

for the registration of the finest details of contour, the breath being held in expiration. Finally, the patient is briefly transilluminated at the end of three, six, twelve, and twenty-four hours, and notes are made regarding (1) the time required for emptying the stomach, (2) the size, shape, position and character of peristaltic waves, (3) any spastic manifestations, (4) the results of attempts to identify pain points, (5) the mobility of the stomach and duodenum, (6) the occurrence of "bismuth flecks," and (7) any special points observable.

(3) *Serial Röntgenography of the Stomach and Intestines*

The method of serial röntgenography that promises to be most helpful in the clinical diagnosis of diseases of the stomach and duodenum has been applied by L. G. Cole. If the intestines are to be studied at the same time—and they always should be—the **technic** advised by Cole is as follows:

At 11 P. M., the patient swallows barium sulphate suspended in buttermilk, and, at the same time, eats a Riegel meal (meat, potatoes and bread). Ten hours later, that is at nine o'clock next morning, a röntgenogram of the whole abdomen is made to see how far the "meal" has progressed, and especially to ascertain with certainty whether or not the ileum is empty. If the ileum still contain barium, a röntgenogram or a röntgenoscopic examination is made bi-hourly until the ileum is completely evacuated. The patient then swallows bismuth or barium suspended in buttermilk. Its passage through the esophagus is observed röntgenoscopically as is its entrance into the stomach. Then the **serial röntgenography of the stomach and duodenum** is begun. Twelve röntgenograms are made in the prone posture, four to six in the lateral direction, two posteriorly, and twelve with the patient erect. After this the patient at once eats a meal of meat, potatoes and bread. Two hours later, another series of 6 to 12 röntgenograms is made, two of them being stereoscopic röntgenograms of the entire gastro-intestinal tract. Four hours after ingestion another series is made. Six hours after the bismuth buttermilk, a pair of stereoröntgenograms is invariably made, and if, at this time, a fluoroscopic view shows any gastric retention, 5 or 6 röntgenograms are made. Next follows the **examination of the ileocecal region.** First two small stereoröntgenograms (8 x 10 in.) are made of this portion of the intestinal tract, and if the röntgenoscopic view reveals marked stasis or any unusual feature, from 6 to 8 small röntgenograms are made. Two hours later, that is at 5 P.M. (or eight hours after the bismuth meal) one plain röntgenogram or one pair of stereoröntgenograms is made, completing the examination for the day.

At 9 A. M. next day, or 24 hours after the ingestion of the barium buttermilk, another röntgenogram is made, and if there be evidence of

colonic stasis or constipation, one röntgenogram is made every 24 hours until the colon is emptied. A patient accustomed to take laxatives regularly is allowed one as usual, but no active purgation is permitted.

To complete the study, a special examination is made for gall-stones and one for spasmodic, or organic, lesions of the colon under mechanical distension.

An active cathartic is given the night before, and, if necessary, a saline early next morning. It is important not to give an enema, since this, if retained, would dilute the barium clyster used to distend the colon.

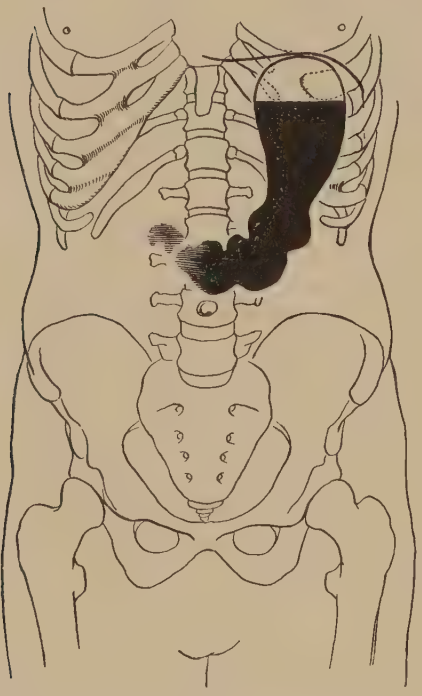

Fig. 332.—Diagram from X-ray of Normal Stomach Taken Immediately After Bismuth Meal. (The Stomach Approaches the Lower Limit for the Normal, and Shows Active Contractions.) By courtesy of Dr. Baetjer and Dr. Waters, X-ray Dept. J. H. H.)

Fig. 333.—Diagram from X-ray of Normal Stomach Taken One Hour After Bismuth Meal and Showing Bismuth in the Small Intestine. (By courtesy of Dr. Baetjer and Dr. Waters, X-ray Dept. J. H. H.)

Before examining the colon, the **examination of the gall-bladder** is made, since gall-stones can now be detected in at least 50 per cent of the cases when they are present, though a negative diagnosis should never be made when there is no evidence of a calculus. The indications of gall-stones may be direct or indirect, the *direct* evidence consisting of a localized area of increased density, of the size and shape of a calculus, while *indirect* evidence is yielded by the distortion of adjacent hollow viscera through

adhesions from an accompanying cholecystitis and pericholecystitis with "hepato-fixation." In making the röntgenograms, a soft tube with brief exposure and intensifying screen are necessary to yield the detail required.

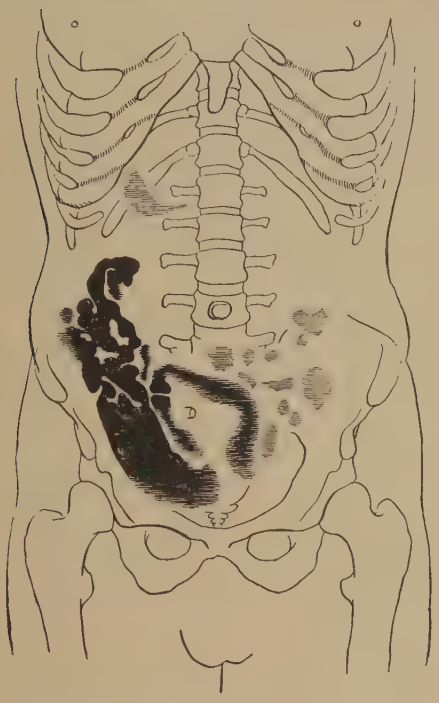

Fig. 334.—Diagram from X-ray of Normal Stomach Taken Five Hours After Bismuth Meal and Showing Bismuth in the Cecum. (By courtesy of Dr. Baetjer and Dr. Waters, X-ray Dept. J. H. H.)

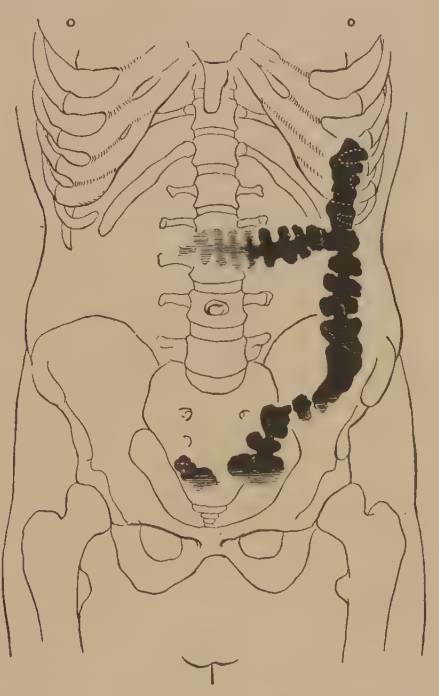

Fig. 335.—Diagram from X-ray of Normal Stomach Taken Twenty-four Hours After Bismuth Meal and Showing Bismuth in the Descending Colon and Rectum. (By courtesy of Dr. Baetjer and Dr. Waters, X-ray Dept. J. H. H.)

A pair of stereoscopic röntgenograms often aid materially in the detection and interpretation of doubtful shadows. In studying the plates, care must be taken to differentiate gall-stones from kidney stones and from duodenal ulcer (see Diagnosis of Gall-Stones).

The **examination of the colon under distension** is next undertaken. A clyster containing barium sulphate, 150 grams, mucilage of acacia, 360 grams, hot water to make 900 c.c. is next administered, and the patient retains it while a pair of stereoröntgenograms of the colon are made. Cole advises making a third plain röntgenogram, or another pair of stereoröntgenograms, as it is sometimes difficult to differentiate between spasms and organic lesions in a single pair of stereoröntgenograms.

The complete examination of the gastro-intestinal tract by this method has, therefore, required a successive series of röntgenograms made immediately after the contrast meal, and at intervals thereafter of 2, 4, 6, 8,

10, 12, 14, 24, 48, and 72 hours, and one or more pairs of stereo-röntgenograms of the colon after the administration of a contrast clyster.

This series, viewed upon a light-box, and studied singly and collectively, yields, Cole asserts, information well worth the trouble and expense involved, since complicated cases, in which the diagnosis by other methods is not possible, can thus be unravelled.

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v. Röntgenology of the Normal Stomach

The form and position of the normal stomach varies markedly, and, before x-ray studies were made, there was much difference of opinion as to whether the oblique, transverse or vertical position is normal. On x-ray examination, it is possible to examine the organ in full function under physiological conditions in living human beings with the stomach full and the patient standing upright. Rieder's studies (1904) led him to conclude that the position of the normal stomach is vertical, the stomach descending from the gas-filled pars cardiaca to form a saclike caudal pole, and, finally, turning upward and to the right to the pars pylorica, the whole stomach thus assuming the form of a **fish-hook,** *pipe*, or *siphon* (Fig. 337). He found nearly all of the stomach in the left half of the body, only the pyloric part passing to the right of the middle line.

Holzknecht's studies (1905) convinced him that, in the normal stomach, the pylorus occupies the lowest position, lying at a level a little above the navel. The normal stomach, he maintained, has the form of a *segment of a circle curved in three planes* like a **cow's horn,** the apex being at the pylorus and the broader end at the pars cardiaca, the cardiac third lying vertically, the narrower pyloric end lying horizontally. Though this form of the stomach exists in only 20 per cent of the persons examined, he believed it to be the normal form, "since out of it all variations and pathological forms can be easily deduced, and since it represents the optimum for the function of the stomach." He admits that the majority of patients (80 per cent) have stomachs that approximate in form the fish-hook type of Rieder, but asserts that this is due to moderate enteroptosis; the stomach normally rests upon a cushion of the small intestine, and, in enteroptosis, this cushion descends so that the stomach assumes the more vertical fish-hook type; thus, from the original, obliquely-situated, normal stomach there arises a vertical stomach.

Size of the Normal Stomach.—The cubic contents of a "cow-horn stom-

ach" are obviously somewhat smaller than those of a "fish-hook stomach." According to Holzknecht, the normal cow-horn stomach can receive three-quarters of a liter easily, and without feeling of tension ("voluntary

Fig. 336.—Röntgenogram of Normal Stomach: Patient Prone; Plate Anterior. (a) Pylorus; (b) First Part of Duodenum (Bulbus duodeni; Cap); (c) Peristaltic Waves; (d) Indentation Partly Due to the Pressure of the Spleen and Partly Due to Pressure of the Gas-filled Splenic Flexure. (Courtesy of Dr. Jas. T. Case.)

capacity" of the stomach). The more distended the stomach, the greater its capacity, which may reach $1\frac{1}{2}$ liters or more.

The lowest point of the cow-horn stomach on standing lies between

the navel and the xiphoid process, that of the fish-hook stomach just beneath the navel.

In describing the fish-hook form of stomach, the following terms are employed (Groedel). The silhouette is divided into a *descending limb* (containing the "stomach bubble" at its top), and an *ascending limb,* consisting of antrum and sphincter antri, and ending at the pylorus. The lowest point of the stomach is called the *caudal pole,* the highest point (under the left diaphragm), the *cranial pole.* The distance between the two poles is called the *height* of the stomach, while the distance of the pylorus from the caudal pole is called the *"lifting height"* (*Hubhöhe*) of the stomach. The connecting line is known as the *longitudinal diameter* of the stomach, and the angle between this and the mid-line as the *angle of inclination* of the stomach.

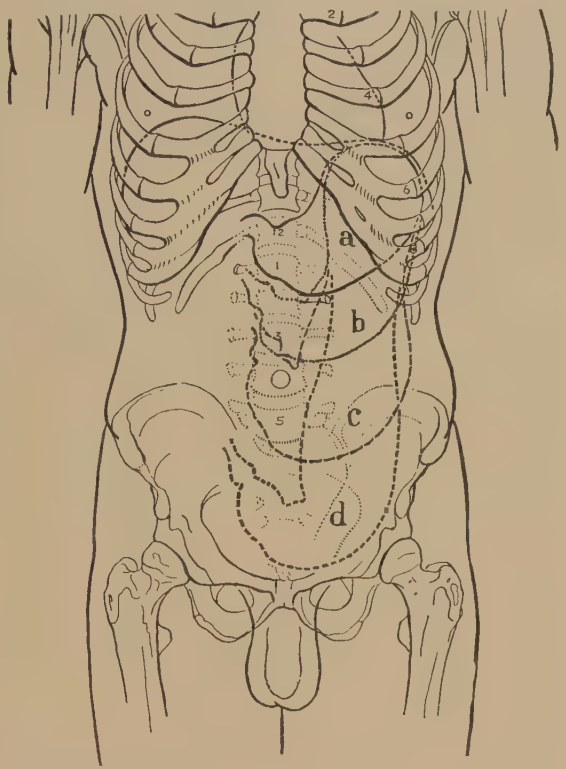

Fig. 337.—Types and Positions of the Human Stomach. (A) Normal Type—Pylorus Is the Lowest Point, No Pulling up of the Pylorus. (After Holzknecht.) (B) The Usual Longitudinal Position Without Sagging. (Rieder's Normal Form.) (C) Moderate Sagging. (Gastroptosis.) (D) Marked Sagging. (Gastroptosis.)

During inspiration, the stomach is pressed downward by the diaphragm; during expiration, it rises so that the position of the cardia and of the pylorus depends upon the level of the diaphragm. Simultaneously with this change in level, the stomach, during inspiration, becomes less perpendicular and more oblique, since the total contents of the abdominal cavity are diminished on inspiration.

On changing from the recumbent to the standing position, the stomach, with the diaphragm, descends. On retraction of the abdominal walls, the stomach rises for a distance equal to its full breadth or more, a point of great diagnostic importance (Holzknecht), for, if the stomach be anywhere adherent to the abdominal wall, this movement will be restricted. In the right and left lateral positions of the body, the caudal part of the stomach moves to the right and left, respectively, from gravity.

The contents of the stomach on röntgenoscopic view can, normally, be promptly moved in all directions by palpation through the abdominal walls. Wherever the wooden spoon or finger presses in (from the side, or from the surface), the contents promptly move in all directions, and a clear area, corresponding in size and shape to the "distinctor" or "palpatorium" used, appears upon the screen. If the stomach wall be greatly infiltrated (inflammation, tumor), this phenomenon may not be observable.

Behavior of the Normal Stomach Before, and During, Filling.—The main features have been carefully described by Holzknecht and Jonas. The empty stomach appears collapsed, with the exception of the region of the stomach bubble; when a little of the bismuth suspension passes through the cardia, the shadow can be seen to glide through the gas bubble, on its medial side, to the pars media, where it remains for a time, as this part only gradually opens. The bismuth collects in the upper part of the pars media, beneath the gas bubble, in the form of a *funnel*, and, later on, slowly flows downward to collect at the caudal pole in the form of a *crescent*. The level of this crescent gradually rises until finally the lesser curvature is reached; in the fish-hook stomach, the filling now takes the form of a *U-shaped tube*, the left limb of the U corresponding to the pars media, the right limb to the pars pylorica. On further filling, the caudal pole does not descend much, but the distension of the stomach occurs transversely rather than vertically.

In the fish-hook stomach, as the two limbs fill, the shadow stands higher in the descending limb, owing to the hindrance to the passage of chyme through the pylorus; for, at the moment the bismuth enters the stomach, the pylorus closes, to open later on, during the expulsion period, rhythmically every twenty-two seconds. The so-called gastric cycles, marked by a systole and a diastole, have been carefully studied by L. G. Cole, and will be described further on under "Motility of the Stomach."

There is *no fixed position to the pylorus*. When the patient stands upright, in both the fish-hook type and the cow-horn type, the pylorus stands at a variable level. Further, it is sometimes in the mid-line, sometimes to the right of it. It changes in position a little during respiration; and it can be dislocated by voluntary retraction of the abdominal wall or by palpation with the hand or with the "distinctor" from without. *The fixed point is really the upper knee of the duodenum*, that is, the point of junction of the horizontal part or cap with the descending part of the duodenum; this is why, in visceroptosis, the pylorus can sink with the stomach when the latter is distended.

The peristalsis of the stomach and the emptying of the stomach are described under "Motility of the Stomach" (*q. v.*).

Reference

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vi. Röntgenology of the Enlarged Stomach (Ptosis; Atony; Dilatation)

The *cow-horn stomach* is a small stomach. The *fish-hook stomach* is elongated, and its caudal pole lies at a lower level (enteroptotic relaxation). There may also be pyloroptosis here, with marked change of position. **Gastroptosis** is, therefore, as Holzknecht emphasizes, not a dislocation downward, with retention of normal form (as in the kidney), but, owing to the slightly movable cardia and the immovable duodenal fixed point, it consists (1) of a slight sinking of the cardia, of the pars cardiaca, and of the pars media, (2) of a more marked sinking of the pars pylorica, and (3) of a most marked sinking of the junction between the two latter, so that *an outspoken hook form results through longitudinal stretching of the cow-horn form.*

In **atony of the stomach,** the preliminary hindrance to filling at the upper part is absent, and the material collects at once in the caudal part, while the pars media remains empty and collapsed (*weakness of muscle tonus* or of peristolic function). The gas bubble in the atonic stomach is strikingly large; furthermore, the atonic stomach is late in emptying itself. (For more on Atony and Hypertony of the Stomach see Motility.)

The *normal breadth* of the stomach, measured at right angles to the long axis of the stomach (not of the body), is about three, or at most four, finger breadths. A transverse breadth larger than this, say a hand's breadth, is certain evidence of a transverse distension, or in other words, of a **dilatation of the stomach.** A dilated stomach of varying degree is not an uncommon finding in chronic gastric or duodenal ulcer. In pyloric or in juxta-pyloric ulcer with stenosis there may be a dilatation of the stomach involving chiefly the antrum pylori, and yielding a very characteristic x-ray appearance described by Cole as "prognathian."

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Holzknecht* (*G.*).** *Enteroptose und Magenerweiterung; Relaxatio ventriculi. Mitt. a. d. Lab. f. radiol. Diagn. u. Therap. im k. k. allg. Krankenh. in Wien, Jena,* ***1906, *i, 88–106.*

vii. Röntgenology of the Small Stomach

The normal *cow-horn type* is, as has been said, physiologically small. The *child's stomach* is small, and may be either of the cow-horn, or of the siphon form.

In pathological states, a **diminution in the size of the stomach** may be due to *cicatricial contraction.* In such cases, the organ is smaller than

the smallest normal stomach, and may be as small as one's fist. A markedly ptotic stomach may, as a result of a contracting process, reach a size smaller than before, though still larger than normal; we then deal with a "relatively small stomach," recognizable by the high level of its caudal pole when the relaxation of the abdominal walls would naturally be accompanied by a lower level for the caudal pole.

A small stomach due to *inanition* is met with in esophageal carcinoma.

In the *cirrhotic stomach,* due either to chronic gastritis, or to scirrhous cancer, the stomach may become extremely small; the contents cannot be displaced on palpation, peristalsis is absent, and the jagged inner surface cannot be distended by increasing the amount of bismuth swallowed.

Displacement of the stomach by tumors, a pregnant uterus, tympanites, etc., might be taken for diminution in the size of the stomach, but careful clinical and x-ray examination easily differentiate. It is usually easy to determine whether a stomach is displaced by being pressed aside (tumor, ascites, pregnancy, etc.), or by being pulled to one side (adhesions from pericholecystitis, appendicitis, omental hernia, etc.).

viii. Anomalies in the Filling of the Stomach on X-ray Examination

Three anomalies have to be considered: (1) the stomach may not fill at all; (2) it may fill in two sections that are more or less separated from one another; or (3) there may be circumscribed defects in the filling.

When the **stomach does not fill at all,** the reason may lie either in *pyloric insufficiency* (functional insufficiency, insufficiency due to carcinomatous ulceration at the pylorus, scirrhous carcinoma), or in *gastroenterostomy,* or in *fistula formation.*

When the **stomach fills in the form of two sections separated from one another (bilocular stomach; hour-glass stomach)** one sees at first two crescentic sacs, one cardial, lying under the gas bubble, and one caudal, the connection between the two being either invisible, or visible in the form of a narrow canal of variable length.

The diagnosis of hour-glass stomach, so difficult formerly, is extremely easy by röntgenological methods. Certain technical details should, however, be borne in mind. If the connecting canal is wide, the bismuth may all collect after a time in the lower section. On the other hand, if the connecting lumen be very narrow, the bismuth may not pass, and, remaining in the upper section, a small contracted stomach may be simulated. If the preliminary fluoroscopic examination with a bismuth-water suspension has been made, the condition will not be misunderstood.

Two *varieties of hour-glass stomach* can be distinguished, (1) a true hour-glass stomach, and (2) a false hour-glass stomach.

(1) The *true hour-glass stomach* is most often due (a) to carcinoma, (b) to a penetrating ulcer or a scar of ulcer on the lesser curvature, or (c) to perigastric adhesions.

When due to *carcinoma*, the narrow channel connecting the two sacs of the hour-glass stomach lies in the stomach axis and is much longer than in the sacculation due to penetrating ulcer. As a rule, there is also pyloric insufficiency.

When due to *ulcer on the lesser curvature*, there is often a residue of the barium meal after the sixth hour, and the stoma between the upper and the lower sac lies along the lesser curvature, the outline of the greater curvature being drawn over toward the lesser (Case). The narrowing occurs at one distinct point, and the canal is usually short.

A *penetrating ulcer on the lesser curvature* may cause a sacculation rather than a typical hour-glass stomach. The projecting barium shadow may be merely a small outcropping from the stomach shadow, or it may be a large mass 12-15 cm. long, and 6-8 cm. wide. In typical cases, a small collection of gas, sometimes called a "little stomach bubble," can be seen lying above the localized barium shadow (Haudek). This "Haudek's niche," or "pocket," is an important sign of penetrating ulcer, but it occurs also in inoperable carcinoma of the lesser curvature and, moreover, must be carefully differentiated from a small deposit in a pouch of the esophagus near the cardia (Cole).

Fig. 338.—Perforating Gastric Ulcer, Indicated by Escape of the Bismuth at x. Note Also the "Little Stomach-bubble," or Haudek's Niche. (By courtesy of Dr. Baetjer and Dr. Waters, X-ray Dept. J. H. H.)

When a true hour-glass stomach is due to *perigastric adhesions*, the deformity may be partly spastic and partly organic. Röntgenoscopic examination may determine whether the adhesions and fixation are posterior, connected with the pancreas, or anterior, connected with the liver; in the latter case, the barium shadow moves up and down with respiration; in the former, it is immovable during respiration (Case).

(2) A *false hour-glass stomach*, or so-called pseudo-hour-glass formation, may be due (a) to gas in the splenic flexure of the colon, (b) to external tumor, or pressure of a deformed costal arch, invaginating the stomach, or (c) to spasm of the circular muscle of the stomach, a deep tonic constriction, causing indrawing of the greater curvature, and

producing a sharply outlined localized indentation of the gastric wall, which lasts minutes, hours, days or weeks (*spastic hour-glass stomach*), and most often, though by no means always, is due to erosion or to ulcer. According to J. T. Case, it is often *purely functional as far as the stomach is concerned,* and can be due to any lesion that causes vagus irritation (*e. g.,* gall-stones, duodenal ulcer, adhesions, appendicitis, Graves's disease, paralysis agitans, tabes or hysteria); in such cases, the spasm often yields to atropin, or to anesthesia, and it may fail to appear when the patient stands, though it reappears when he lies down.

When **circumscribed filling-defects** are visible, information of the most important kind for the diagnosis of carcinoma, round ulcer, tuberculosis or lues may be obtained. If a tumor of the wall of the stomach project into the interior, it will occupy a space that cannot be filled by bismuth, and there will be, accordingly, a *defect in the filling* of the stomach in the x-ray picture.

Of course other recognizable causes for such a defect must be absent. Thus the defect must persist on attempts to fill it up by manual or distinctor palpation. And it should be remembered that, in the atonic stomach, the pyloric portion and the pars media may not completely fill except on careful manual compression and change of posture.

When there is a real circumscribed filling-defect, the internal contour may be jagged; moreover, pressure with the finger-tips or the wooden spoon does not lead to a normal dispersion of the contents in all directions. Changes in peristalsis also appear (*q. v.*).

If W. J. Mayo is right in his recent assertion that 36 per cent of cancers of the stomach can be cured by surgical procedure, it is highly important to make an early diagnosis of the condition. Hitherto the surgeons have maintained that an early diagnosis can be made only by surgical exploration, but, fortunately, evidence is accumulating that a negative, or a positive, diagnosis of cancer of the stomach can be made as accurately by serial röntgenography as by exploratory laparotomy (Cole). If this prove to be correct, it will be possible to make the diagnosis of cancer at an early stage in very many patients who would be willing to submit to röntgenography, but who would refuse exploratory laparotomy until the symptoms had passed far beyond the incipient stage.

Advanced growths can, of course, be detected either by röntgenoscopy, or by two or three röntgenograms taken by the ordinary methods, but the recognition of early carcinoma, and the positive ruling-out of the existence of carcinoma (so-called negative diagnosis), demand at present a complete serial röntgenographic examination, such as Cole has devised (see above). Carcinoma, adenoma, myoma, sarcoma and indurated ulcer yield röntgenographic signs indistinguishable from one another, which is not surprising when it is recalled that a surgeon is frequently uncertain at operation which he is dealing with, and has to await the report

of the microscopic examination before deciding. Fortunately, the surgical indications are, at present, the same for all.

The röntgenographic diagnosis of cancer (and of masses indistinguishable from cancer requiring surgical removal) is based upon permanent, constant, deformities in the wall of the stomach that interfere with the systole and diastole of the stomach, and with the progress of peristaltic waves toward the pylorus. If the gastric lesion is extensive, a permanent filling-defect in the wall will be visible, but the diagnosis of early lesions has to be based rather upon interruption of peristaltic contractions (see Motility), than upon filling-defects.

The character of a filling-defect, in cancer, depends upon the nature

Fig. 339.—Tumor Mass in Greater Curvature of Stomach. Inoperable Carcinoma Found on Laparotomy. 1. Filling Defect on Greater Curvature; 2. Greater Curvature; 3. Pylorus. (X-ray Dept. J. H. H.)

and form of the growth. The commoner findings have been well summarized by Cole. Thus, a *large round mass* projecting into the stomach will yield a characteristic corresponding filling-defect, the area being constant in size, shape and position in a series of röntgenograms. If there be *multiple nodular growths*, a peculiar, "finger-print" appearance is often seen in the röntgenogram; such growths are common on the pos-

terior wall and may cause obstruction, though patients suffering from this type of growth are often singularly free from symptoms. In *annular growth*, advancing in the form of a cone, the barium shadow presents a characteristic "funnel-shaped" appearance, the apex being drawn out to a small constricted lumen containing barium, the lumen sometimes becoming finally completely obliterated; in such cases peristaltic contractions cease abruptly when they reach the involved area, and there may be a worm-eaten appearance with overhanging edges at the line of the invasion. It is important to note that the constricted lumen remains constant in size, shape and position, and shows no rugae such as are present in normal tissue and as are often exaggerated in cases of perigastric adhesions and pylorospasm. In *scirrhous cancer*, instead of a filling-defect, the diagnosis often has to be made upon (1) the high position and small size of the stomach (*q. v.*), and (2) the absence of peristaltic contractions or the evidences of abortive peristalsis with broad waves.

A beginning carcinomatous ulcer of the pylorus or of the duodenum may be indistinguishable röntgenographically from duodenal ulcer.

It is often possible to say immediately, from the röntgenographic examination, whether or not a tumor is an inoperable or an operable one. Its exact size, location and state of mobility can be determined. Inoperable cases can be saved from unnecessary exploratory laparotomy, and operable cases can be sent to the surgeon early.

A *positive, or a negative, diagnosis of ulcer* of the stomach or of the first portion of the duodenum (cap) can now be made with great accuracy, some think with as great accuracy as the diagnosis of a fracture of a bone, or of a renal calculus (Cole). The disturbances of motility upon which such a diagnosis is based are referred to farther on. Such accuracy can be gained, however, only when complete serial röntgenography of the whole gastro-intestinal tract is undertaken, for we now know that remarkable changes in the motility of the wall of the stomach and duodenum, sometimes leading to permanent changes in the pylorus, the pyloric sphincter, and the cap, may depend upon lesions entirely outside the stomach (ileal stasis and dilatation, chronic appendicitis, colonic lesions, gall-bladder lesions, adhesions, etc.). As Cole emphasizes, the röntgenologic method of diagnosis should not be discredited by erroneous diagnosis dependent upon abbreviated methods.

Bismuth Flecks Representing Ulcer-craters Filled with Bismuth

An idea is prevalent among physicians that bismuth will stick to the crater of an ulcer and will cast a shadow visible on the röntgenoscopic screen or in the röntgenogram; but experience proves that it is rare for an ulcer to reveal itself in this manner. It is true that in penetrating

ulcers on the lesser curvature and in ulcers of the duodenum such a bismuth fleck is sometimes demonstrable. The peculiar appearance of penetrating ulcer of the lesser curvature with more or less sacculation of the stomach wall, and with the formation of a minute stomach bubble, as described by Haudek, has been referred to above. Flecks in the duodenum should be most carefully scrutinized, however, before it is assumed that they represent deposits in the crater of an ulcer, for, otherwise, duodenal ulcer may be confused with any one of several other conditions. Thus a bismuth fleck in the ampulla of Vater, a stone in the right kidney, a small gallstone, or a bismuth-residue in the gall-bladder in cases of cholecystenterostomy, may be mistaken for ulcer of the duodenum (J. T. Case). Further, it should not be forgotten that, normally, a small portion of bismuth may persist in the first portion of the duodenum, that is, in the cap, for some time after the stomach has completely emptied itself. When there is doubt, the examination should be repeated.

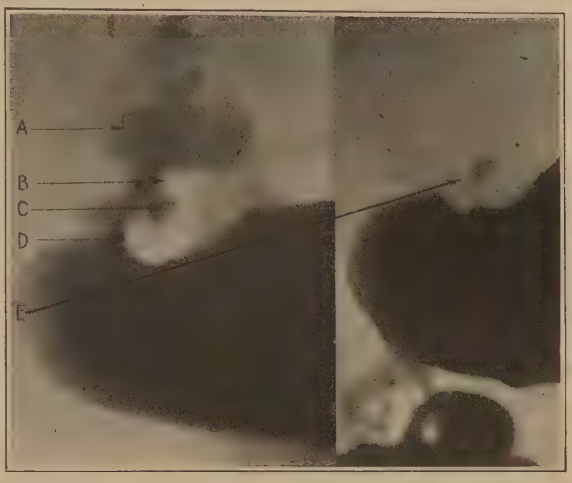

Fig. 340.—Röntgenogram Illustrating a Bismuth Fleck in the Crater of an Ulcer. (B) Profile of Ulcer. (C) Crater of Ulcer. (D) Everted Edge of Ulcer. (E) Fleck of Bismuth in Crater of Ulcer. (After L. G. Cole, The Lancet.)

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(c) *Examination of the Motility of the Stomach*

Introduction

As has been pointed out above, two special functions have to be considered in studying the motility of the stomach: (1) the peristolic function and (2) the peristaltic function.

These motor phenomena have been carefully studied in the stomachs of small animals (cats, dogs) by W. B. Cannon, by Roux and Balthazard, and by Lommel. In human beings they have been studied in this country by Baetjer and Waters,

Ashbury, L. G. Cole, J. T. Case, George and others; and in Europe, important studies were undertaken by Rieder, Holzknecht and Brauner, Groedel, Jolasse, Hertz, Kästle, Schwarz and Kreuzfuchs.

The **peristolic function** has to do with the tonus of the stomach, and, in judging it, we are guided largely by (a) the *form of the stomach when filled*, as revealed by the x-ray, and (b) the *way in which the stomach fills* when the bismuth or barium suspension is swallowed (*vide supra*). This peristolic function has been referred to, and a description of the manner in which the stomach normally fills, and of the deviations from this normal filling met with in pathological states, has been given above.

The **peristaltic function** has to do with (a) the *mixing* of the ingesta with the stomach-juice and (b) the *expulsion* of the chyme into the duodenum, at frequent intervals, during gastric digestion. In judging of this peristaltic gastric motility, *two principal methods* are at our disposal: (1) the direct *observation of peristaltic waves*, on the fluoroscopic screen, in serial röntgenograms, or by röntgenocinematography; and (2) the time required for the stomach to empty itself—so-called "*emptying time*," (a) after a bismuth meal or a barium meal, as determined by x-ray examinations, and (b) after a test supper, or a test meal during the earlier part of the day, as determined with the aid of the stomach tube.

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ii. Rontgenology of the Peristalsis of the Stomach

Peristalsis in the Normal Stomach.—To study the peristaltic activity of the stomach and the systole and diastole of each gastric cycle, the barium-buttermilk should always be administered in conjunction with a Riegel meal of meat, potatoes, and bread. The patient should be examined röntgenoscopically in several postures; usually, the peristaltic phenomena are best seen when the patient is on his back.

A distinction must be drawn between the peristalsis of the pars media and that of the pars pylorica. Usually, as soon as the bismuth or other contrast material is swallowed, but more markedly after the stomach has been filled, indentations become visible more or less high up on the greater curvature of the pars media of the stomach, and these indentations can be seen passing as waves toward the pylorus, the waves gradually increasing in depth as they advance. These waves on the greater curva-

ture, however, can be seen to stand still, suddenly, at a point of deep indentation; and, opposite to the latter, a similar indentation, though less deep, can be seen to mark the end of a peristaltic wave on the lesser curvature, the two indentations together forming a deep constriction around the stomach at the level of the muscle of the pyloric antrum. The peristaltic waves of the body of the stomach are not propagated further toward the pylorus, that is, into the antrum itself. The latter undergoes concentric contractions of itself (peristolic function).

These concentric contractions of the wall of the pyloric antrum are sometimes spoken of as "terminal waves, or contractions." They are short, deep and rhythmical, and, aside from their constant increase in depth, they are equal, following one another, usually, at intervals of about twenty-two seconds, often without intermission from the time the bismuth is swallowed until the stomach is finally emptied. Cole asserts that the time occupied for the formation of each "terminal wave" of the antrum corresponds to a *cycle* of the motor activity of the whole stomach, the activity of the stomach, like that of the heart, showing a period of systole and one of diastole for each cycle. During *systole* there is a contraction of all the waves (peristaltic and terminal) simultaneously, and during *diastole,* a relaxation. During systole, which occupies seven-tenths of the cycle, chyme is expelled through the pylorus into the duodenal cap or "pilleus ventriculi"; during diastole (the remaining three-tenths of the gastric cycle), the pylorus is closed by the M. sphincter pylori, and this prevents the chyme in the cap from dropping back into the stomach. According to the rate per minute of these cycles, Cole speaks of stomachs of the three-cycle and of the four-cycle type.

The peristaltic function appears to be supported at the end by a strong peristolic contraction; this is the so-called "final contraction" of Schwarz and Kreuzfuchs. Between the fasting stomach, and the stomach that has just emptied itself, there was believed to be a distinct difference; for in the latter, the caudal pole stands at a higher level than in the former, and this high position appears to be due to a state of contraction occurring in the walls of the stomach at about the end of the expulsion time. Some believe that this "final contraction" is a variation, in the atonic stomach, of a normal process that consists of an evenly progressive contraction of the stomach during the expulsive period through a gradual increase of the normal tonus. Thus, in the cow-horn form of stomach the "final contraction," it is said, does not occur. It was thought to be limited to the stretched fish-hook form, and was therefore regarded by Holzknecht as a delayed peristolic expulsion contraction, and as an evidence of atonic insufficiency.

Peristalsis of the Stomach in Pathological States.—Hyperperistalsis and hypertonicity are both very suggestive of duodenal ulcer. Hyperperistalsis of the stomach is also observed (1) in pyloric insufficiency (functional, ulcerative), (2) after gastro-enterostomy, and (3) in gastro-intestinal fistula. Increased frequency of the waves, beginning of the

waves high up on the greater curvature, and marked depth of the waves, at first thought to indicate pyloric stenosis, are now known not necessarily to do so, though it is admitted that in atonic dilatation of the stomach, the peristalsis is usually strikingly feeble. The administration of HCl increases the activity of gastric peristalsis, while the administration of olive oil diminishes it.

Arrest of the peristaltic wave, or sudden and marked diminution of the wave occurs in regions infiltrated with cancer or other neoplasm.

Spasm of the antrum pyloricum, of the M. sphincter pylori, and of the duodenal cap is common, and may be due (1) to disease of the stomach itself or (2) to disease of the duodenum, gall-bladder, ileum, appendix, or colon (reflex spasm). The spasm may be directly observable röntgenoscopically or in serial röntgenograms, or the results of the spasm may be discoverable as a permanent reduction in the size of the lumen.

Thus in spasm of the antrum pyloricum, the lumen may be reduced in size out of all proportion to the dimensions of the pars media and the

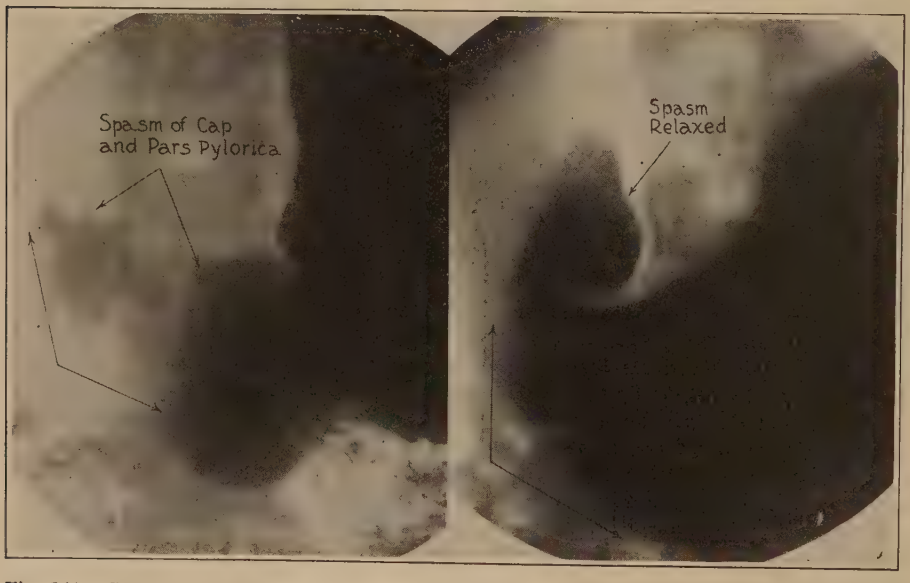

Fig. 341.—Spasm of the Cap and of the Pyloric End of the Stomach Due to Reflex Spasm in a Case in which the Stomach Was Normal But Chronic Appendicitis Existed. (After L. G. Cole, Am. J. Röntgenol.)

pars cardiaca, the lumen assuming a corrugated appearance owing to the formation of deeper folds of the mucosa than normal. In serial röntgenograms, one plate may show extreme puckering, while a later one taken during relaxation of the spasm may show a smooth, well-distended contour. In spasm of the M. sphincter pylori, the barium may tempo-

rarily disappear from the lumen of the sphincter and cap though earlier and later it is abundant there. In spasm of the pars superior duodeni (the cap), there is a characteristic appearance; the distorted lumen yields a "corrugated or fluted shadow" in röntgenograms. This appearance might easily be mistaken for chronic indurated duodenal ulcer, but if serial röntgenograms be made, one or more will be obtained in which a fully-distended and well-defined cap is visible if the condition is due to spasm and ulcer is absent (Cole). When long-continued spasm leads to permanent changes in these parts, röntgenographic evidence will not be wanting in the form of permanent puckerings, lack of pliability, and broad peristaltic contractions, though a regular systole and diastole may still be exhibited.

When duodenal peristalsis is inhibited—say in ileal stasis—there may be retention first in the cap and later in the antrum pyloricum and stomach, even when there is no pylorospasm.

Antiperistalsis, first röntgenoscopically observed by Jonas, is believed to be pathognomonic of an organic lesion at the pylorus, or near it. The lesion need not cause obstruction, though often it does do so. Antiperistalsis may be an important criterion in the differential diagnosis between atony of the stomach and stenotic dilatation. Thus, in pyloric stenosis, no matter whether it be due to cicatrix from ulcer, or to carcinoma, waves can sometimes be seen to pass from the antrum pylori in a reverse direction, that is toward the cardia, the indentations due to the wave deepening as the wave advances. The symptom is not observable in all cases, but, when visible, it appears to be a reliable early symptom in pyloric stenosis. It must be admitted, however, that antiperistalsis is a comparatively rare phenomenon, as some röntgenoscopists say they have never seen it.

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iii. Determination of the Time Required for the Stomach to Empty Itself (Expulsion-Time or Emptying Time)

Röntgenographic studies indicate that a stomach of the cow-horn type, after an ordinary bismuth subcarbonate meal, empties itself in about two hours, while a stomach of the fish-hook type, according to its length (just above, or just beneath, the umbilicus), usually empties itself in from four to six hours. If a longer period than six hours be required for complete emptying, a pathological disturbance of motility is believed to exist.

The use of barium sulphate shortens the emptying-time, in normal cases, to within 3 or 4 hours (Groedel).

In some cases, especially when food is taken regularly after a Rieder bismuth meal, more than twenty-four hours elapse before the bismuth is entirely removed from the stomach. This is regarded as a certain indication of pyloric stenosis. An emptying time of seventy-two hours, or even 150 hours, has been observed in pyloric stenosis.

Motor insufficiency of the stomach is thus readily demonstrated röntgenologically. The rule was early laid down that when, after a half liter of milk porridge to which 30-40 grams of bismuth have been added is swallowed, the stomach requires more than six hours to empty itself, motor insufficiency exists, and the longer the delay in emptying itself, the

greater the degree of motor insufficiency. As to the diagnosis of insufficiency of the second degree (*stasis insufficiency*) by the x-ray, an emptying-time of at least twenty-four hours, or more, must be observed before we can be sure that pyloric stenosis exists. The longest emptying time in *motor insufficiency due to atony* alone, thus far observed, is sixteen hours.

There has been much discussion as to whether *ulcer* of the stomach can exist without pylorospasm and a lengthening of the emptying-time beyond six hours. Haudek has asserted that an emptying time longer than six hours invariably indicates serious alteration of the stomach

Fig. 342.—Hypermotility with Shortened Emptying-time of the Stomach in Duodenal Ulcer. Röntgenogram 15 Minutes After Bismuth Was Ingested. Note the "Filling Defect" Indicating the Site of the Ulcer in the Shadow of the Duodenal Cap. (By courtesy of Dr. Baetjer and Dr. Waters, X-ray Dept., J. H. H.)

wall, but later röntgenological and surgical experience does not support this view. Many surgical operations have been undertaken on the basis of this hypothesis, and no ulcer found. Further, ulcer can be present when there is no delay in the emptying time; Smithies has reported 100 of these cases.

A **shortened emptying-time** when not due to achylia gastrica is very suspicious of irritation in the right upper quadrant (duodenal ulcer, gall-bladder disease, adhesions). Baetjer and Friedenwald, Case, and Cole have emphasized this point, and their views are now shared by most röntgenologists. In duodenal ulcer, the stomach often begins to empty itself immediately, clearance going on at a very rapid rate, the stomach sometimes being entirely empty at the end of one hour. If the bismuth meal be large, the clearance may be slower, owing to a delayed pylorospasm. If a small barium meal be given in duodenal ulcer, and rapid clearance fail to follow, it is evidence of mechanical obstruction due to cicatricial contraction.

In ulcer of the pylorus, the emptying time is usually lengthened owing to hypersecretion and early pylorospasm. In ulcer of the body of the stomach, the emptying time may be normal.

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iv. Examination of the Motility of the Stomach by Means of the Stomach Tube

Since Kussmaul's introduction of the stomach tube into the medical clinic in 1867, intubation of the stomach has been much employed both in the diagnosis and in the therapy of gastric disease.

(1) *Technic of Passing a Stomach Tube (Gastric Intubation)*

A soft tube of red rubber about 12 mm. in diameter, with either a solid or open end, but with oval openings on each side near the end, is used. The tube introduced by Ewald is especially suitable. It may be lubricated with warm water, glycerin or butter. The patient, with a towel or a rubber sheet about his neck, sits in a chair, leans his back against the back of the chair, and inclines his head slightly forward. The examiner, standing to the right of the patient, holds the proximal end of the tube and the aspirating bulb in his left hand, which may also give gentle support to the back of the patient's head. With his right hand, the distal end of the tube is held in pen fashion. The tube is now passed through the patient's mouth to the uvula. The patient is then asked to swallow, and, as he does so, the tube is gently pressed

toward the esophageal opening. By slight rotation, it is usually easy to make it enter the esophagus, after which, standing in front of the patient, the examiner finds it easy to pass it downward into the stomach. The patient is then told to close the mouth and to bite the tube gently. The tube is next held, close to the teeth, by the examiner's left hand, while with his right hand he compresses the aspirating bulb and attaches it to the tube. If the patient now open his mouth so that the lumen of the tube is reëstablished, the stomach contents will flow through the tube, and the intercalated glass tube, into the bulb.

If the stomach contain but little, it may be necessary to move the tube slightly, in and out, to start the aspiration. If the opening be plugged, a little air may be blown in. When enough has been extracted, the tube still attached to the aspirating bulb is withdrawn, the left hand grasping the tube near its distal end and compressing it to prevent leakage.

As in the passage of esophageal bougies, one should make sure, before passing a stomach tube, that aneurism of the aorta does not exist. Other contra-indications to the passage of the tube are, (1) severe cardiac disease, (2) a very high arterial pressure, and (3) recent hemorrhage from the stomach.

On intubation of nervous patients, the tube may accidentally be shoved into the larynx and start a violent coughing reflex; this rarely happens, however, and is not a dangerous accident, as the tube can be immediately withdrawn. Some patients tend to hold the breath, even when the tube has passed properly; they should be told to breathe deeply and regularly so as to avoid any feeling of suffocation.

If there be difficulty in aspiration, the abdomen may be gently massaged to start the flow, or the patient may lie down flat on a couch and let his head hang over the side. The various ways in which the stomach tube can become kinked and interfere with removal of the stomach contents have been carefully studied in röntgenograms by Harmer and Dodd (1913).

(2) *Application of Gastric Intubation to Motility Studies*

In testing the motor function of the stomach by means of the tube, the idea is to determine how much of the food ingested has been emptied from the stomach at the end of a given time. Two difficulties are encountered: (1) it is not easy to remove the contents absolutely without residue, and (2) we do not know in what proportions the food residues and the gastric secretions exist in the stomach contents obtained (W. Wolff). Two methods have been introduced in which the attempt is made to separate the functions of motility and secretion more accurately; one is the *method of determining the residue* advocated by Mathieu and Rémond,

the other is the *butyrometric method* devised by Sahli. Both are interesting for special researches, but neither is yet of practical value.

Useful results can be obtained as follows:

One passes the stomach tube in the early morning, the patient having taken no food since the night before, when he should have taken an ordinary mixed meal. The patient is asked to make pressure with the abdominal muscles for the purpose of expressing the gastric contents, or the physician may attempt manually to express them. If no stomach contents appear, a half liter of warm water is then poured through a funnel placed in the tube into the stomach. This funnel should be held somewhat obliquely to avoid the entrance of too much air. The fluid is allowed to flow in slowly until all the water except that at the lower end of the funnel has gone in. The funnel and the tube are then quickly lowered so that by means of the water remaining in the stem of the funnel and in the tube, a siphon action is started, the stomach thus being washed out. Should the stream stop before the stomach has been emptied, the patient can often start it by contracting the abdominal muscles firmly. If much food has remained in the stomach, the flow may be frequently stopped, owing to the lodgment of particles in the openings of the tube; in this event, it may be necessary to wash them out by pouring in more water and starting the siphoning process over again. The use of a syringe for injection, or of a vacuum-bulb for aspiration, as described above, may be used if desired, though most gastrologists advise avoidance of the aspirating bulb for fear that the gastric mucous membrane will be injured; sometimes, pieces are torn away from the gastric wall. Should the method of clearing the tube above mentioned prove unsuccessful, it is better to withdraw the tube for cleansing, and then introduce it again. The lavage is continued until the stomach is empty, and the fluid that comes away is clear.

Some authors recommend the addition to the evening meal of a tablespoonful of currants, of raspberry jam, of other seedy fruits, or of boiled rice, to facilitate the discovery of food residues next morning (Strauss's currant test). Wolff recommends a "test supper" consisting of one portion of rice, some veal, and a saucer of cranberries (*Preiselbeeren*). With this technic the tube may, if desired, be passed after breakfast, instead of upon the fasting stomach, provided no seeds are taken with the breakfast itself. With the method described, we discover whether food taken say 12-14 hours earlier has all left the stomach, or whether a retention exists. Normally, on passing the tube in the morning, fasting, no food residue should be found. The finding of food means retention; if the food residue is visible to the naked eye, we speak of **macroretention,** if only microscopically, of **microretention.**

Even when the fasting stomach is empty, this does not prove that the gastric motility is normal. Some stomachs may possess feeble motility, though the gastric

muscle may be able to empty the organ of a definite amount of food by the end of twelve hours. It is important, therefore, to use the Riegel test meal or the Ewald or Dock test breakfast (*q. v.*), which are employed for testing the chemical and secretory functions of the stomach, also in testing for disturbances of motility. If, after a Riegel test meal, the stomach is not empty at the end of seven or eight hours, a disturbance of motility exists. The same is true if the stomach is not empty two hours after an Ewald or a Dock test breakfast. When applying these tests of motor function, the test breakfast should be given in the morning, and the test meal at the time of day when the patient is accustomed to take, ordinarily, his largest meal.

The above methods are very helpful when the röntgenological methods already described cannot be employed.

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v. Indirect Tests for Motility (Without Passage of a Stomach Tube)

If for any reason it is neither feasible to pass a stomach tube nor to make an x-ray examination of motility, it may still be possible to secure some evidence regarding the motility of the stomach by *indirect testing* of the function. For this purpose a salol test (Ewald and Sievers), an iodoform test (Fleischer), an iodipin test (Winkler and Stein), and a sodium phosphate test (Roux and Laboulais) have been devised. None of them is, however, entirely satisfactory; they should be resorted to only when better methods are inapplicable.

The Salol Test of Ewald and Sievers for the Motor Power of Stomach.—Salol, which is chemically the salicylate of phenol, is neither split into its components, nor absorbed, in the stomach. Only after it has entered the intestine is it broken up into phenol and salicylic acid. The latter, after its formation, is absorbed and is excreted in the urine as salicyluric acid, easily recognizable by the violet color that appears on the addition of a solution of ferric chlorid to the urine.

Capsules containing one gram of salol are given with a test breakfast, and the urine is examined every ten minutes thereafter for salicyluric acid. Normally, the reaction appears first at the end of thirty minutes, never later than seventy-five minutes. A delayed appearance of the reaction was thought to point to motor insufficiency of the stomach. A draw-back to the method lies in the fact that when the stomach contains an excess of mucus, or when pancreatic juice is regurgitated

into the stomach, the salol may be split and absorbed before it leaves that organ. For this reason, it has been recommended by Huber that the period of retention of salol by the stomach—that is, the time when the salicyluric-acid reaction *disappears* from the urine—be measured. When the motility of the stomach is normal the salicyluric-acid reaction disappears by the twenty-seventh hour. Accordingly, the patient, emptying the bladder at the end of twenty-seven hours, is asked to pass urine every three hours, thereafter until the salicyluric-acid reaction, if still present, disappears. The delay of the end of the reaction is said to be directly proportionate to the slowing of motility of the stomach. One can easily combine the two methods, determining, in the first place, the time of first appearance of the reaction, and, in the second place, the time of disappearance of the reaction in the urine.

Fleischer's Iodoform Test for Motility of the Stomach.—Instead of salol, one may give a capsule of 0.1 g. iodoform with, or just after, the main meal. With normal gastric motility, iodin is demonstrable in the urine in from 1 to $1\frac{3}{4}$ hours.

vi. Degrees of Motor Insufficiency of the Stomach

It is customary to divide the cases of motor insufficiency into three degrees of severity, though no hard and fast lines can be drawn.

First Degree, or Slight Motor Insufficiency.—Food residue is found in the stomach seven hours after a Riegel test meal. Or, in the fasting stomach, in the morning after a test supper, a slight microscopic food residue, or even a trace of macroscopic residue, is found.

Second Degree, or Medium Motor Insufficiency.—Definite macroscopic food residue is found in the fasting stomach, though the stomach may, to a large degree, have emptied itself.

Third Degree, or Severe Motor Insufficiency with Stagnation.—The stomach always retains a large amount of residue, almost nothing being passed into the duodenum. Residues of food taken several days before the examination may be found.

Measurements of the daily amount of urine voided will often throw light upon the **degree of dilatation** of the stomach and the accompanying motor insufficiency. Water is not absorbed from the stomach, but only from the intestines, and the non-absorption of water may therefore indicate the degree of motor insufficiency. Boas, therefore, divides the stages of gastric dilatation, according to the urine passed.

First Stage.—Daily quantity of urine between 1,500 and 1,000 c.c.
Second Stage.—Between 900 and 500 c.c.
Third stage.—Less than 500 c.c.

vii. Causes of Motor Insufficiency of the Stomach

An inability of the stomach to empty itself may be due, (1) to *primary* muscle weakness in the stomach-wall, often associated with atony;

this is called *primary* or *atonic motor insufficiency,* and is common in acute and chronic gastric catarrh; or (2) to *secondary* muscle weakness, especially that following pyloric stenosis, either benign or malign, causing dilatation of the stomach (gastrectasia); this is called *secondary motor insufficiency,* or *stasis insufficiency.*

The motor disturbance in chronic gastritis rarely exceeds the first degree; the secondary insufficiencies correspond to the motor insufficiencies of severer grades.

(*d*) *Examination of the Secretory and Digestive Functions of the Stomach*

In order to test the secretory and digestive functions of the stomach, a systematic procedure is desirable, including, (1) the examination of the contents of the stomach obtained by passing a tube in the early morning in the fasting person, and, in case residue is found, washing out the stomach, followed by (2) the administration of a test breakfast, or test meal, on an empty stomach, with physical, chemical and microscopic examination of the stomach-contents removed at a definite time after such administration.

i. Examination of the Contents of the Fasting Stomach

Normally, the stomach should be found empty when a tube is passed in the early morning in the fasting person. Should more than 30 c.c. of fluid be found in the stomach, the condition may be regarded as abnormal.

In pyloric stenosis and impaired motility large quantities of food ingested on the preceding day (or earlier) may be found in the fasting stomach (See Tests for Motility, already described).

In continuous hypersecretion, sometimes known as gastrosuccorrhea, or Reichmann's disease, the fasting stomach may contain considerable quantities (30-500 c.c.) of a thin, clear, watery fluid without admixture of food particles. Microscopically, a few leukocytes and epithelial cells may be found in it. Chemically, the findings may be similar to those of normal stomach juice, or there may be a hyperacidity.

If there be doubt as to whether the large amount of fluid is due to a nervous hypersecretion or to motor insufficiency, the question can be decided by washing the stomach out, thoroughly, in the evening, and then passing a tube early next morning, the patient fasting, to ascertain whether or not the stomach is still empty. If large amounts of fluid are then found in the morning, with a normal, or more than a normal, acidity, we have to deal definitely with hypersecretion. [Just here, I desire to call attention to the frequency with which small lumps of sputum, swallowed during the night, may be found in the juice removed in the early morning

from the fasting stomach. In beginning apical tuberculosis, bacilli may, not infrequently, be demonstrable in such sputum.]

The Clinical Significance of the Contents of the Fasting Stomach

The clinical conclusions that may be drawn from the findings of the contents removed from the fasting stomach have been well summarized by W. Wolff as follows:

I. **Normal amount** (up to 20 c.c.): capable of forming drops, mucoid, reaction neutral or acid. Microscopically: leukocytes, epithelial or "free nuclei" and spirals = *without diagnostic importance.* It must be remembered, however, that even though the amount be normal, micro-retention may exist!

II. **Increased amount:**

(a) *Without food residue:*

(1) Forming drops more easily, containing HCl. Microscopically: free nuclei "and spirals" = *gastrosuccorrhea,* met with in neuroses and in ulcers of the stomach.

(2) More mucoid, reacting neutral or alkaline. Microscopically: leukocytes and epithelia = *gastromyxorrhea*, met with in healthy people, and in those suffering from various diseases, especially gastric catarrh.

(b) *With food residue:*

(1) HCl present. Microscopically: many starch cells, some muscle fibers, "free nuclei," yeast, sarcinae, occasionally CO_2 or H_2S-fermentation = *motor insufficiency with retained secretory power*, met with in cases of gastric ulcer or the scars from ulcer, especially when situated at the pylorus. Simultaneous admixture of bile makes obstruction beyond the pylorus (ulcus duodeni) probable.

(2) Reaction neutral, or alkaline. Microscopically: some muscle fibers, a few starch granules, some budding yeasts, many leukocytes and cocci (occasionally tumor cells) = *motor insufficiency with loss of gastric secretion,* met with in gastric catarrhs, and, especially, in beginning carcinoma of the lesser curvature.

(3) Acid reaction, lactic acid present. Microscopically: starch granules, many muscle fibers, yeasts, Oppler-Boas bacilli = *motor insufficiency with lactic acid fermentation,* met with almost exclusively in carcinoma ventriculi (at the pylorus).

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ii. The Administration of Test Breakfasts and Test Meals

If the fasting stomach be found empty, a test breakfast may be administered at once; should it be found to contain food residues from the day before, or more than 30 c.c. of fluid, the stomach should be washed out with warm water before the test breakfast is given.

The advantage of giving a test breakfast of definite composition is to have a basis for comparison and for the establishment of a normal. The secretion of stomach juice varies so much with the varieties of food taken that, unless some standard test-food is administered, the results of the examination of the stomach juice could scarcely be profitably valued.

(1) *Varieties of Test Breakfast*

White Bread Test Breakfast (Ewald).—This consists of a dry roll weighing about 35 grams, or an equivalent amount of white bread (without butter). In addition, two cups of weak tea (300-400 g., without milk or sugar), or of water, are swallowed.

Shredded Wheat Test Breakfast (Dock).—This is the same as Ewald's, except that one shredded wheat biscuit is substituted for the roll of white bread. This breakfast contains no lactic acid; the latter, or a substance yielding a similar reaction, is occasionally present in traces in white bread.

Oatmeal Test Breakfast (Boas).—This consists of one tablespoonful of oatmeal, boiled in 800 c. cm. water until the volume is reduced to 400 c.c. It, too, is free from lactic acid.

Dry Test Breakfast (Boas).—This consists of five Albert cakes masticated thoroughly, and taken without fluid of any sort.

(2) *Time of Removal of the Stomach Contents*

The stomach tube is passed by the method already described (*q. v.*) at the height of gastric digestion (one hour after ingestion of the test breakfast), and the contents subjected to examination. At the end of two hours after such a test breakfast, the stomach is, normally, again empty.

Recently, interest has been shown in the so-called continuous study of the gastric secretion after a test breakfast, or a test meal. A small tube is left in the stomach and at regular intervals the stomach contents are aspirated for examination. Such studies have been prosecuted in this country especially by Rehfuss and Hawk of Philadelphia, and in Europe by Ettinger. The results are, in many instances, surprising,

and it is probable that hitherto we have often been deceived as to the secretory activities of the stomach by limiting ourselves to single examinations of stomach contents after the test meal.

Such test breakfasts as those given above represent the simplest and most convenient form of test diet, and require the least expenditure of time on the part of the patient. The examination of the stomach contents obtained after such a test breakfast permits us to draw conclusions, not only regarding the secretion, but also reading the motility of the stomach. Test breakfasts, however, make only relatively slight demands upon the functional capacity of the stomach. In order to draw conclusions regarding the power of the stomach to meet the demands of the everyday diet, a larger meal, such as that of Riegel, is necessary.

(3) *Varieties of Test Meals Other Than Test Breakfasts*

Test Meal (Riegel).—This consists of 400 grams of beef broth, 150-200 grams of beefsteak, 50 grams mashed potato, and one roll (35 grams), or an equivalent amount of white bread. Instead of the quantities of mashed potato and roll above given, the roll may be omitted and 150 grams of mashed potato given. The stomach should be entirely empty when the test meal is eaten. The stomach contents are removed for examination in from three to five hours after ingestion. At the end of seven hours the stomach is, normally, again empty.

Riegel's test meal is, perhaps, less important for testing the secretory power of the stomach than for testing the motility of that organ. This test meal has the advantage of corresponding to the demands that every day diet makes upon the stomach. A stomach that can manage a test breakfast perfectly well may show signs of failure with a test meal, though this is rare. It is often, however, very inconvenient to give a test meal; first, on account of its constituents, and, second, on account of the fact that it should be given at the time when the main meal of the day is ordinarily taken, and the stomach contents should not be removed for examination until at least three hours afterward; indeed, since we use it less for testing the secretion than for testing the motility, it is scarcely worth while to attempt its removal before seven hours. (See Motility Tests.)

Fischer's Test Meal.—In this country, instead of Riegel's meal, a meal consisting of the bread and water of the Ewald, or Dock, breakfast, together with a quarter of a pound of finely chopped lean beef, broiled and slightly seasoned, is sometimes given and removed after three hours (on testing secretion), or after seven hours (on testing motility).

Test Supper (Boas).—This consists of 100 grams of white bread with a little butter, and cold meat, together with two cups of tea with sugar. The addition of currants, rice, raspberry jam, etc., to such a test supper has already been described. (See Tests for Motility.) The

patient takes the meal at supper time, and the tube is passed next morning fasting.

Many other test meals have been recommended, but the above will be found entirely sufficient for every day clinical work.

iii. Examination of the Stomach Contents Removed after Test Diets

The contents of the stomach removed after a test diet consist of (1) food, (2) secreted stomach-juice, (3) mucus, and (4) fluid transudate. During digestion, the mixture is constantly undergoing change, as a result of the secretory, motor, and absorbent functions of the stomach. The examination is divisible into three parts: (1) macroscopic examination; (2) microscopic examination; and (3) chemical examination.

(1) *Macroscopic Examination of the Stomach Contents*

Here we pay attention to (1) the general appearance, (2) the color, (3) the amount, (4) the odor, and (5) the quantity of mucus.

General Appearance.—After a test breakfast the contents, normally, separate into two parts, (1) fine bread particles, which fall to the bottom as a precipitate, and (2) a turbid fluid lying over the precipitate. If the stomach contents be poured into a graduated cylinder, the relative volume of the two layers can be read off. Normally, the volume is as 1:1, or the "layer coefficient" = 1. This separation into two layers may not occur if much mucus is present.

If there has been an excessive secretion (hypersecretion), the amount of fluid is increased and the sediment is finer—the layer coefficient > 1. If the secretory activity be diminished (hyposecretion; achylia gastrica), the consistence is that of a thick, greasy gruel, often running with difficulty through the stomach tube, and large fragments of undigested bread may be visible; the layer coefficient $\wedge$ 1. The appearance of the stomach contents in achylia gastrica and in hypersecretion are so characteristic that simple inspection may permit the skilled observer to recognize at once the fact that these secretory disturbances exist.

When pyloric stenosis exists the stomach contents removed next morning after a test supper separate on standing into three layers: (1) an uppermost, frothy layer, containing some undigested particles; (2) a middle layer of turbid fluid, and (3) at the bottom, a sediment consisting of fine starch granules.

Color.—After a test breakfast, there should be, normally, only the bread particles and a slightly greenish, watery, clear, fluid. In pathological cases, an abnormal color is often seen due to the admixture of blood, of bile, or of pancreatic juice.

Blood, when present, may be due to trauma from the tube, especially in achylia gastrica (if due to atrophy of the mucous membrane, in which

case the gastric mucous membrane seems to be particularly vulnerable). In ulcer of the stomach, and in carcinoma, the color may be dark red, or brownish black—coffee-groundlike—owing to the presence of altered blood.

Occult blood in the stomach juice is tested for by the same methods as are used for the feces (See Examination of Feces), but the following points should be remembered: (1) The presence of blood in vomitus is of no value for diagnosis; vomitus in at least half the cases contains blood, usually due to the trauma of vomiting. (2) The presence of blood in stomach contents removed after a test breakfast is of very little value for diagnosis, often leading to diagnostic errors, since slight hemorrhage from trauma is exceedingly common. We rely, therefore, rather upon the demonstration of the presence of occult blood in the feces. Obviously, the feces should not be examined for blood too soon after the passage of a stomach tube.

When traumatic hemorrhage can be ruled out, the presence of occult blood in the stomach juice most often points to carcinoma, though it may be due to ulcer. It is almost never present in gastric catarrh.

For the diagnosis of ulcer (benign or malignant) at the pylorus, M. Einhorn has introduced what is known as his thread test for occult blood, a silk thread of sufficient length being swallowed at night, the proximal end being fastened to the cheek by a strip of adhesive plaster. Next morning the thread is removed and blood-staining looked for. If found, the distance from the incisor teeth is measured.

Bile and pancreatic juice are often found in stomach contents, especially when the patient empties the fasting stomach by contraction of his abdominal muscles in conditions favoring regurgitation from the duodenum through an open pylorus. The stomach contents may then present a golden yellow, or a grass green color (bile pigments, or their oxidation products). The finding is of no practical value, except in the rare instances in which it is constantly present along with stagnation residue in the fasting stomach, when it indicates stenosis of the duodenum below the papilla of Vater.

Bile and pancreatic juice can nearly always be obtained in the stomach juice after the administration of 200 grams of oil on an empty stomach, and the method is sometimes employed in the study of pancreatic function (*q. v.*).

A rose-colored stomach juice may be due to the presence of urobilin, the clinical significance of which is, as yet, in dispute.

The Amount of Stomach Contents.—This depends partly upon gastric motility, partly upon gastric secretion. On the one hand, the greater the motility, the less the amount, and *vice versa;* on the other hand, the greater the secretion, the greater the amount, and *vice versa.* Ordinarily, after a test breakfast, from 50-100 c. cm. of stomach contents are obtained on removal.

The amount of stomach contents obtained is not a very safe criterion from which to form judgments, however, since only a part of the stomach contents is actually removed by the tube; a portion always remains in the stomach. Various attempts have been made to estimate this residue. The principle underlying these methods is simple. After removal of as much as possible by the stomach tube, an exactly measured amount of water is poured through the tube into the stomach, mixed as intimately as possible with the residue there, after which the stomach contents are again expressed; by utilization of the acidity of the contents first expressed and the acidity of the second specimen, the amount of the residue is determined ("residue-determination" of Mathieu-Rémond, of Straus-Elsner, and of Hayem and Winter). The method is circumstantial, and, clinically, rarely of importance. The same may be said of the ingenious butyrometric method of Sahli.

The Odor of the Stomach Contents.—Normally, the stomach contents, removed after a test diet, have a *sour* smell. The same smell is present in hyperacidity. In subacidity, or anacidity, and when mucus is abundant, the odor is *stale.*

In benign pyloric stenosis with protein putrefaction, there may be an *odor of hydrogen sulphid;* a strip of filter paper saturated with alkaline lead acetate solution will turn black when suspended in a closed vessel over such a juice.

A *fetid smell* may point to ulcerative carcinoma; a *feculent odor* to fistula connecting the stomach with the colon, or to intestinal obstruction.

The Amount of Mucus in the Stomach Contents.—Moderate amounts of mucus are not abnormal. Absence of mucus (*amyxorrhea gastrica*) makes the stomach abnormally vulnerable to hot fluids, or to irritating chemical substances in the food, and probably favors hyperchlorhydria and ulcer; indeed, in cases of existing ulcer, complete absence of mucus is common. It should be recalled that some of the mucus present may have been swallowed (sputum, nasal or pharyngeal catarrh), in which case, the "foreign" masses of mucus appear as isolated balls in the fluid, and are not intimately mixed with the food particles.

In some cases, enormous amounts of mucus of gastric origin may be present (*myxorrhea gastrica*)—a symptom of catarrhal gastritis (primary, or secondary to ulcer, carcinoma, etc.). The amount of mucus is best judged by pouring the sediment from one glass into another and observing its stickiness and coherence.

(2) *Microscopical Examination of the Stomach Contents*

The main features have already been discussed under the microscopic examination of the vomitus (*q. v.*). For clinical purposes, the demonstration of the presence or absence of (1) Oppler-Boas bacilli, and

(2) particles of mucous membrane, or tumor, are the most important. The presence of pus cells, of red blood corpuscles, of starch granules, of yeasts, of sarcinae, of crystals, etc., and their significance, have already been referred to.

Eosinophile cells are occasionally met with, especially in achylia gastrica. Infusoria of several varieties (Trichomonas, Balantidium, Lamblia, Cercomonas) have been observed but rarely (see Examination of Feces).

The long, thread-shaped bacilli known as the **Oppler-Boas bacilli** have some diagnostic importance. Their appearance in stomach contents stands in a certain relation to the formation of lactic acid. The bacilli may appear as short rods, 6-8 microns long, but in active lactic acid fermentation they become long, thread-shaped forms. They are facultative

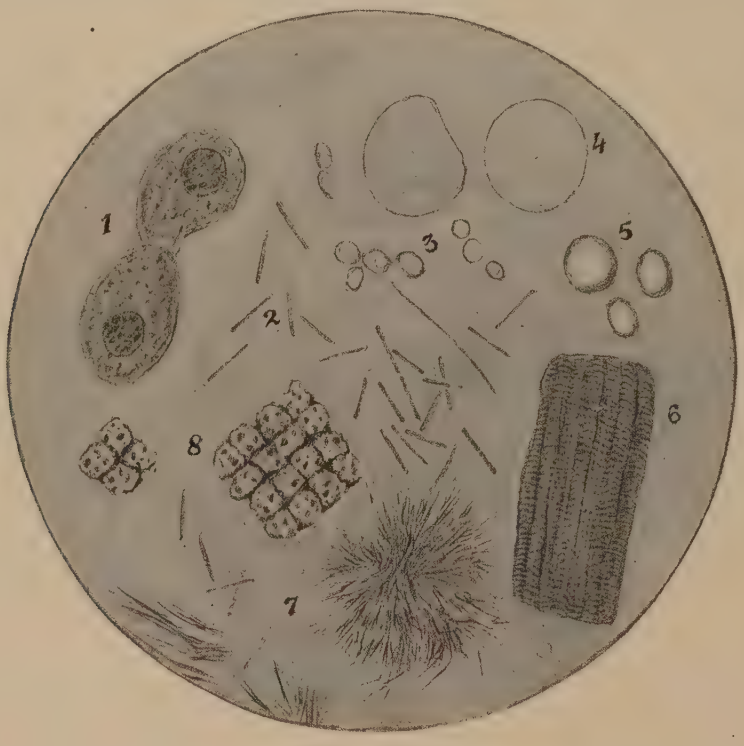

Fig. 343.—Gastric Contents—Composite Picture. 1. Epithelial Cells; 2. Oppler-Boas Bacilli; 3. Yeasts; 4. Starch Granules; 5. Fat Droplets; 6. Muscle Fiber; 7. Fatty-acid Crystals; 8. Sarcinae.

anaërobes. Their growth is arrested in the stomach when the hydrochloric-acid content is as much as 0.3-0.5 per cent. In order that they may multiply freely, there must therefore be diminished secretion of HCl along with a severe disturbance of the motility, leading to stagnation of food. Since this combination of stagnation and secretory insufficiency occurs

almost exclusively in carcinoma ventriculi, the presence of large numbers of the long bacilli is of diagnostic importance. The bacilli may be absent in cases of carcinoma that have not caused severe disturbance of motility and stagnation. A few isolated bacilli are of no importance in diagnosis; only when enormous numbers are present, filling the microscopic field, is the sign significant.

Small **particles of gastric mucous membrane, or of tumors** should be carefully sought for. They are macroscopically recognizable by their grayish red color. They should be placed in a fixing fluid at once, then hardened, sectioned, and examined microscopically. Particles of mucous membrane may show atrophic or inflammatory changes. Tumor particles may make the diagnosis of carcinoma, or, more rarely, of sarcoma or of polyp, certain.

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(3) *Chemical Examination of the Stomach Contents*

Chemically, we study the *acids* and the *ferments* in the stomach contents. This study includes: (1) the determination of the reaction of the stomach contents, (2) qualitative and quantitative determinations of the acids in the stomach contents, (3) qualitative and quantitative determinations of the ferments normally present in gastric secretion, (4) the making of certain other tests that bear upon the diagnosis of carcinoma of the stomach.

(1) **Reaction of the Stomach Contents.**—The reaction of the fluid

is tested with blue litmus paper. Normally, this is turned red, owing to the presence of acid, that is of hydrogen ions, which belong to the free and combined HCl and the acid salts (phosphates) of the secretion.

Even in the absence of HCl, the stomach contents may yield an acid reaction, owing to the presence of organic acids (lactic acid, butyric acid, acetic acid, etc.), which have resulted from abnormal fermentation of the stomach contents. In the absence of such fermentation products and of HCl, the reaction is neutral. An alkaline reaction may be present when there are large quantities of mucus in the stomach contents, or when there has been a regurgitation of alkaline duodenal contents (bile, pancreatic juice) into the stomach.

(2) **The Acids in the Stomach Contents.**—We have next to determine what components are responsible for the acidity of the stomach contents. The *total acidity* (Aciditas totalis = **A**) is composed of (1) hydrochloric acid (**HCl**), (2) organic acids (**O**), and (3) acid salts (**S**); expressed as a formula: **A = HCl + O + S.** The HCl is, in turn, composed of (1) "free" mineral acid (acidum hydrochloricum liberum = **L**), and (2) hydrochloric acid in loose combination with protein, known as acid albumin (acidum hydrochloricum combinatum = **C**); the full formula, therefore, reads: **A = L + C + O + S.**

When **L** is present, **O** is negligible, since free HCl inhibits the fermentative processes through which the organic acids are formed. The acid salts (**S**) consist chiefly of acid phosphates; they are derived from the food ingested, and being practically constant, in minimal quantity, for a given test breakfast, need not be determined quantitatively; as a rule this quantity varies between 2 and 6 "acidity per cent." If the stomach contents are acid to litmus, we proceed to the making of (1) qualitative tests for free HCl and for organic acids, and (2) quantitative determinations of (a) the total acidity (= **A**), (b) the free HCl (= **L**) and (c) the combined HCl (= **C**). If no free HCl be present, we may desire to determine (d) the so-called "HCl deficit" (see below), and (e) the presence or absence of combined HCl (= **C**).

Qualitative Tests for the Presence of Free HCl

In practice, it is very important to know whether, or not, free HCl is present in the stomach contents, for, when present, it is an indication that the secretory function of the stomach is good, and it makes the presence of lactic acid or of other organic acids due to fermentative processes improbable. There are many color reactions for determining the presence of free HCl qualitatively. Among these, the following three are the more important:

1. **The Red Congo-paper Test.**—This paper, of a rose-red color, turns intensely blue when moistened by stomach contents containing free HCl.

If free HCl be absent, the color remains unchanged; if only small amounts of free HCl be present, a bluish violet tint appears.

Other mineral acids behave like HCl, but they are never present in the stomach juice. Organic acids (lactic acid, etc.) do not change the color of congo paper, at least in the concentrations in which they are met with in stomach contents.

2. **Günzberg's Reagent (Phloroglucin-vanillin Test).**—This reagent is the most reliable one at our disposal for the demonstration of the presence of free HCl. It consists of 2 grams of phloroglucin, 1 gram vanillin, and 30 grams of absolute alcohol.

To apply the test, one or two drops of the reagent and a similar amount of filtered stomach contents are brought together on a porcelain dish and cautiously warmed over a flame, care being taken not to burn or even to over-heat the preparation. If free HCl be present, the part first becoming dry, as the fluid evaporates, turns red at the edges, and, soon, a beautiful red mirror appears on the surface that has been wet. No attention should be paid to a brown, or to a yellow, color; only a bright red color is of value as a positive reaction. The reagent should not be too old when it is used, and it should be kept in a brown glass bottle. The test is delicate, yielding a positive reaction in stomach contents containing as little as 0.05 per cent of free HCl.

3. **Dimethylamidoazobenzol.**—This substance in 0.5 per cent alcoholic solution, a light yellow fluid, known as Töpfer's reagent, is also turned red by free HCl. It is much used as an indicator in quantitative determinations (see below). It is not, however, a reagent for free HCl solely, for it will also react to certain highly-ionized combinations of acid and protein, of acid and peptids, and of amino acids (F. W. Rolph).

Other qualitative tests for free HCl, such as the resorcin test of Boas, and the methyl-violet test of van den Velden, are superfluous.

Quantitative Determinations of the Acids of the Stomach Contents

By testing the amount of HCl present in stomach contents at a definite time after a test diet, we obtain results that are of value for comparison. It is of course impossible to test, quantitatively, the exact amount of HCl secreted during any definite period of digestion, for we have no means of telling how much of the stomach juice has already been passed through the pylorus into the duodenum. The relative measure that we use, however, is of great value clinically, though no attention should be paid to slight deviations from the average, for persons vary considerably, in the amount secreted, according to age and race.

Psychic influences may affect secretion. The food ingested has a marked effect, meat increasing the secretion of HCl, fat inhibiting it. Only marked deviations

from the average, found to exist on repeated examinations, are to be regarded as abnormal.

Determination of the Total Acidity (= A) of the Stomach Contents.—To determine, quantitatively, the total acidity of the stomach contents, we use the method of titration, as follows: Ten c.c. of the filtered stomach-contents, taken up by pipet, are placed either in a porcelain dish, or in an Erlenmeyer flask over a sheet of white paper. A drop of 1-per-cent alcoholic solution of phenolphthalein is added as an indicator, the addition causing a slight whitish turbidity. As is well known, this indicator remains colorless in neutral and in acid solutions, but turns to a brilliant pink or red color as soon as the reaction becomes just alkaline. From a graduated buret, an $\frac{N}{10}$ NaOH solution is then run in, the beaker being constantly shaken until the pink color, which appears after each new drop, ceases to disappear on shaking.

We express the total acidity in "acidity degrees" for 100 c. cm. of stomach contents; in other words, we multipy the number of cubic centimeters of $\frac{N}{10}$ NaOH solution used by 10, since we have used only 10 c. cm. of stomach contents in our test. Thus, if 6 c. cm. of $\frac{N}{10}$ NaOH solution have been required to neutralize 10 c. cm. of stomach contents, the stomach contents have an acid value of $6 \times 10 = 60$ acidity per cent, or 60° of acidity.

The normal total acidity after a Dock, or an Ewald, test breakfast is 30-60 acidity per cent, after a Riegel test meal, 70-100 acidity per cent.

A convenient indicator-method of determining the total acidity of the stomach contents will be described further on.

Quantitative Determination of the Free HCl (= L) in the Stomach Contents.—The most exact methods of determining quantitatively the free HCl of the stomach contents consist in titration with $\frac{N}{10}$ NaOH solution until the qualitative color reactions for HCl disappear. Thus, in the *Mintz-Fleiner method*, one uses Günzberg's reagent as the indicator. In the *Mörner-Boas method,* an aqueous solution of congo red is used as the indicator.

For practical, every day work, however, the *method of Töpfer* is much more convenient, and is the one usually used. There are, however, some objections to its use (See below).

Method of Töpfer.—Ten c.c. of stomach contents, in which the presence of free HCl has been demonstrated, are titrated with $\frac{N}{10}$ NaOH solution, a few drops of a 0.5-per-cent alcoholic dimethylamidoazobenzol

solution (Töpfer's reagent) being used as indicator. This indicator yields a red color when free HCl is present. The titration is continued until the red color disappears (reappearance of original yellow tint). The number of cubic centimeters used to produce this end reaction is multiplied by 10 in order to give the amount of $\frac{N}{10}$ NaOH required to neutralize the free HCl in 100 c. c. of stomach contents; the product is the "acidity per cent" of free HCl (= **L**) present in the stomach juice. If now, a few drops of 1-per-cent phenolphthalein solution be added to the yellowish fluid, one can go on titrating with $\frac{N}{10}$ NaOH solution until the fluid turns red, indicating alkalinity. The total number of cubic centimeters of $\frac{N}{10}$ NaOH solution used from the beginning, multiplied by 10 will give the total acidity (= **A**) for 100 c.c. of stomach juice. For example, if the $\frac{N}{10}$ NaOH in the buret stood at first at 10 c. cm. and the red color of the dimethylamidoazobenzol turned to yellow when the level of the fluid in the buret fell to 7.5 c. cm., then 2.5 c. cm. were required to neutralize the free HCl in 10 c. cm. of stomach contents, and, multiplying by 10, the free HCl acidity per cent (or **L**) = 25. Now, if to the same fluid, phenolphthalein be added, and it requires the running in of $\frac{N}{10}$ NaOH from the same buret until the fluid has fallen to the mark 5.2, to yield a pink color, the total acid in 10 c.c. of stomach juice has required 4.8 c. cm. of $\frac{N}{10}$ NaOH for neutralization and the total acidity per cent (or **A**) = 48.

Citron's Acidometer.—For quick clinical work, say in a physician's office, this little instrument is very convenient and sufficiently accurate. It consists of a calibrated tube, which is filled with filtered stomach contents as far as the mark (M). Two drops of a reagent (composed of 1 part dimethylamidoazobenzol, 1 part phenolphthalein, and 10 parts alcohol are then added. $\frac{N}{10}$ NaOH is added drop by drop until the color turns yellow (free HCl), and then more until the color turns red (total acidity). The acidity percentages of each (**L** and **A**) are read off directly on a scale.

F. W. Rolph, of Toronto, asserts that Töpfer's reagent is not a reagent for free HCl, but reacts also to certain highly ionized combinations of acid with proteins, peptids, etc. He believes that in judging of superacidity, it is better to titrate against tropeolin, since it is the acid that ionizes sufficiently to react to tropeolin that, in some manner, produces the symptoms of superacidity and tropeolin can be used to measure that superacidity.

Quantitative Determination of Combined HCl (= C) in the Stomach Contents.—*Rough Approximation.* To return now to our formula:

$$\mathbf{A = L + C + O + S}$$

Since free HCl is present, the **O** component (or organic acids) is practically negligible, entirely so if the Dock test breakfast be used; and **S** (or acid salts) is small, varying between 2 and 6 acidity per cent. We can therefore roughly calculate **C** (or the combined HCl) by subtracting **L** and **S** from **A**. Thus $\mathbf{A - L = C + S}$, or $48 - 25 = 23$; the acidity per cent of combined HCl will then be from 2 to 6° less than 23, that is 21 to 17. For ordinary practical work, this estimate is close enough.

Determination by Titration With an Alizarin Indicator.—The combined HCl can, however, be determined as follows: **A** and **L** are determined as above. Then a second portion of 10 c. cm. of filtered gastric juice is titrated with $\frac{N}{10}$ NaOH solution, using a 1-per-cent aqueous solution of alizarin-monosulphonate of sodium as an indicator. When 2 or 3 drops of this violet indicator are added to 10 c.c. of filtered gastric contents, the mixture assumes a yellow color. Alizarin is made yellow by free acids (both mineral and organic) and by acid salts, but not by organically bound HCl. Thus in the stomach juice mixed with alizarin, the color remains yellow until **L, O** and **S** have been neutralized, when it again turns violet. The $\frac{N}{10}$ NaOH is run in from a buret until the stomach juice takes on a pure violet color that does not deepen on the further addition of the alkali.

Some practice is necessary before the end-point of titration can be accurately determined, since the color passes from yellow through a faint violet to pure deep violet (free from red!).

The exact color of the end-point can be observed in a test tube in which a few drops of alizarin solution are mixed with a 1-per-cent solution of sodium carbonate (R. W. Webster); this can be used as a control during titration as the end-point is approached.

The amount of $\frac{N}{10}$ NaOH needed to titrate 100 c.c. of stomach contents with alizarin as an indicator corresponds to $\mathbf{L + O + S}$, and if we subtract this amount from the total acidity (**A**), as determined by titration against phenolphthalein, we shall have the acidity per cent of the combined HCl (= **C**).

$$\mathbf{A - (L + O + S) = C}$$

If, now, we add this combined HCl to the free HCl, as determined by

titration against dimethylamidoazobenzol as indicator, we shall have the acidity per cent of all the physiologically active HCl, *i. e.*, **L** + **C**.

If we next subtract this factor (**L** + **C**) from the total acidity (**A**), we shall have the amount of organic acid and acid salts present:

$$\mathbf{A} - (\mathbf{L} + \mathbf{C}) = \mathbf{O} + \mathbf{S}.$$

Thus, if the level of the $\frac{N}{10}$ NaOH in the buret after the phenolphthalein titration were 5.2, and it fell on titration with alizarin to 2.3, then $\mathbf{L} + \mathbf{O} + \mathbf{S} = 10 \times 2.9 = 29$.

Thus: $\mathbf{A} = 48$

$\mathbf{L} + \mathbf{O} + \mathbf{S} = 29$

$\mathbf{C} = 19$

or: $\mathbf{A} = \mathbf{L} + \mathbf{C} + (\mathbf{O} + \mathbf{S})$

$48 = 25 + 19 + 4$

As **O** is probably zero or almost zero, **S** is about 4.

The "degree of acidity" (or "acidity per cent") can be easily converted into the actual percentage of HCl in the stomach contents, by multiplying it by 0.00365, since this is the amount of HCl that is neutralized by 1 c. cm. of $\frac{N}{10}$ NaOH solution. Thus, if **L**+**C**=25+19=44, then the stomach contents contain 44×0.00365 or 0.158 per cent HCl or about 1.5 parts per 1,000.

This completes the examination for the acids in the stomach contents when free HCl has been shown to be present. But if free HCl be absent, a different procedure is required. First, we determine the total acidity (**A**) by titration with phenolphthalein as indicator. If this is found to be between 0 and 6, it may be fully accounted for by acid salts (**S**); then we may assume that **C** = 0, in other words that the stomach is not secreting HCl at all. Should, however, the total acidity be greater than 6° (or acidity per cent), then we must determine the so-called "hydrochloric acid deficit."

Quantitative Determination of "HCl Deficit."

If free HCl be absent, though combined HCl is present, one can get a clew to the degree of the secretory disturbance by determining the amount of HCl that must be added to the stomach contents in order that the qualitative test for free HCl can be obtained.

To 10 c.c. of the filtered stomach contents, we add $\frac{N}{10}$ HCl solution until a reaction for free HCl appears, *i. e.*, until all the proteins present are "bound" to HCl, and some HCl remains free. As indicator we can use Töpfer's reagent, the end-point being when the yellow fluid turns red.

But it is better to use either congo paper or Günzberg's reagent to determine the point at which free HCl appears.

The number of cubic centimeters of $\frac{N}{10}$ HCl used, multiplied by 10, will give the acidity degrees of the HCl deficit in 100 c.c. of stomach contents.

The value obtained for the HCl deficit can be used, also, to determine the amount, if any, of bound HCl (= **C**) present, that is, whether any HCl at all has been secreted and if so how much. To get at this, we should know the maximal quantity of HCl that the protein and the amino acids present can bind. If we subtract from this, the HCl deficit found, we obtain the amount of HCl that has actually been secreted and bound. Now the maximal amount of HCl that can be bound by the stomach contents depends upon the amount of proteins and other bases present. It has been shown that the ordinary test breakfast (Dock, Ewald) contains an approximately constant amount of these substances, so that after a test breakfast, a fairly constant amount of HCl is bound. In 100 c.c. of filtered stomach contents this corresponds to 20 c.c. of $\frac{N}{10}$ HCl; that is to say, if no HCl were secreted by the stomach, it would be necessary to add to 100 c.c. of filtered stomach contents 20 c.c. of deci-normal HCl solution in order to satisfy all the protein and bases present. The value of 20 then represents the maximal HCl deficit possible after a test breakfast as far as the protein in the test breakfast itself is concerned. If we then subtract the HCl deficit actually found from 20, we have the value for the combined HCl present in a given specimen.

To cite an example: If 10 c.c. of filtered stomach contents, shown to contain no free HCl by the fact that red congo paper is not turned blue, be placed in a beaker, and a little distilled water and 1 or 2 drops of Töpfer's reagent (dimethylamidoazobenzol) added, a yellow color appears; on adding deci-normal HCl solution, drop by drop, from a buret, it is found that 1.6 c.c. are required before a permanent red color appears. This would correspond to 16 c.c. for 100 c.c. of filtered stomach contents. The "HCl deficit" is therefore 16 and the amount of HCl that has been secreted and bound = 20 — 16 = 4.

In cancer of the stomach, abnormal proteolytic cleavage may occur and give rise to peptones, peptids, and amino acids, which increase the combined HCl at the expense of free HCl. The total acidity may be high without any free HCl being present.

This determination of HCl deficit and of bound HCl should be made in all cases in which free HCl is absent.

Michaelis and Davidsohn's Indicator Method of Determining Total Acidity of the Stomach Contents.—Recently, a method for determining the total acidity of the stomach juice clinically, by a simple system of

indicators that determine the concentration in hydrogen ions, has been introduced by Michaelis and Davidsohn. By using their series of indicators and finding which indicator in the series corresponds to the hydrogen-ion concentration of the solution, a very exact result appears to be obtained.

In each of four test tubes is placed 1 c. cm. of filtered stomach contents, and to each tube a different indicator is added: (1) methyl violet, 0.03 per cent aqueous solution; (2) tropeolin, 0.25 per cent solution in 50 per cent alcohol; (3) congo red, 0.125 per cent aqueous solution; and (4) methyl orange, 0.25 per cent aqueous solution.

The colors are observed by transmitted light and compared with the following table in which the acidity can be read off directly as the number of hydrogen gram-ions per liter.

Table of Colors with Different Indicators and the Corresponding Acidity

Indicators	$0.1_n = 1.10^{-1}$	$0.032_n = 1.10^{-1,5}$	$0.01_n = 1.10^{-2}$	$0.0032_n = 1.10^{-2.5}$
Methyl violet	green	green	green	greenish blue
Tropeolin....	burgundy red	burgundy red	orange	orange
Congo red...	blue, precipitate	blue, precipitate	blue, precipitate	bluish violet, precipitate
Methyl orange	red	red	red	red

Indicators	$0.001_n = 1.10^{-3}$	$0.0001_n = 1.10^{-4}$	$0.00001_n = 1.10^{-5}$	$0.000001_n = 1.10^{-6}$
Methyl violet	blue	violet blue	bluish violet	violet
Tropeolin....	yellow	yellow	yellow	yellow
Congo red...	bluish violet, ppt.	dirty red	red	red
Methyl orange	red	orange	yellow	yellow

Method of Recognizing Beginning Insufficiency of HCl Secretion (Gluzinski).—This method was introduced to determine whether or not an ulcer at the pylorus is undergoing malignant degeneration. According to Gluzinski, the change from a simple ulcer into an ulcus carcinomatosum is always accompanied by the development of a gastric catarrh with pronounced mucus-formation. The mucus neutralizes the HCl secreted, and also inhibits its secretion, so that, in beginning carcinoma, though free HCl may be found in single tests of stomach contents, when

a larger effort is required of the stomach by giving several test meals during one day, free HCl may disappear.

The stomach contents are removed in the morning fasting, after which the stomach is thoroughly washed out, and a special test breakfast given, consisting of the whites of two hard-boiled eggs, finely chopped, with 100-200 c.c. of water. After one hour, the stomach contents are again removed. The patient is then given a test meal at noon, consisting of soup, rare beefsteak, mashed potato and bread, and three hours later the stomach contents are again removed. If the reaction for free HCl is absent in any one of these three tests, Gluzinski asserts that a malignant degeneration of the ulcer is to be assumed. The method appears to have some value, though a positive result is not absolutely pathognomonic for ulcus carcinomatosum.

Qualitative Tests for Organic Acids

In the normal stomach, especially after a Dock test breakfast, lactic acid is never present (except in traces); even in abnormal stomachs, as long as HCl is secreted in sufficient amounts, lactic acid is not found. The presence of lactic acid is therefore a sign, on the one hand, of lack of free HCl, and, on the other, of stagnation of the stomach contents, resulting, as it does, from abnormal fermentative processes due to the action of bacteria. Small quantities of lactic acid may be bound. When present in larger quantities, it exists free in the stomach juice and is a pathological finding of importance, indicating, as it does, a severe motor and secretory insufficiency of the stomach. Such combined motor and secretory insufficiency is most common in cancer of the stomach, so that the presence of lactic acid is almost pathognomonic of malignant disease; I say *almost*, and must emphasize the word, since a certain number of cases have been observed in which lactic acid appeared in the stomach in large amounts, though no malignant disease existed.

Since lactic acid is likely to be present only in stomach contents that have undergone stagnation for some time in the stomach, the stomach contents after an ordinary test breakfast may not be suitable for the test. The same is true of Riegel's test meal. If the presence of lactic acid be suspected, therefore, a test supper should be given in the evening and a tube passed, fasting, in the early morning; if there be stagnation, with absence of free HCl, lactic acid will probably be found in large amounts. Lactic acid itself is odorless; the stench of stomach contents that have undergone fermentation is due to other substances (butyric acid, etc.).

Uffelmann's Test for Lactic Acid: 10 c.c. of a 4 per cent solution of carbolic acid are mixed in a test tube with 20 c.c. of distilled water and 1 or 2 drops of a ferric chlorid solution (10 per cent) added, to give the

mixture a deep amethyst-blue color. On the addition of a few drops of stomach juice containing lactic acid, the blue color disappears, and the fluid assumes a yellowish green tint, especially well seen in transmitted light; a good way is to look down into the test tube held over a white ground.

Roger Morris recommends diluting the test fluid until it is transparent and dividing it equally among three tubes. To the first a few drops of filtered stomach contents are added, to the second a like quantity of distilled water to serve as a negative control, and to the third a little dilute lactic acid solution as a positive control.

Several modifications of Uffelmann's reaction (Fleischer's, Kelling's) have been introduced. Some of them permit of the demonstration of smaller quantities of lactic acid than does the original test, but it is only larger quantities of lactic acid that have any diagnostic significance, and the practitioner will get along well enough if he limit his examinations to the use of the original Uffelmann reaction.

The amount of lactic acid can be quantitatively determined if desired, best by the use of Strauss's separating funnel for preliminary extraction by ether, but such determination has no practical value. The qualitative test alone is of importance for diagnosis. Color reactions similar to that yielded by lactic acid may occur with substances like alcohol, citric acid, tartaric acid, etc., but these are not present after a test breakfast.

Other organic acids may occur in the stagnating stomach contents. *Butyric acid* is usually recognizable by its "rancid" odor, and it or *acetic acid* may be specifically tested for if desired (See Text-books of Chemistry); but such tests are of no clinical advantage.

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(4) *Ferments in the Stomach Contents*

On examining the stomach contents for ferments we have to consider (1) the ferments of the normal stomach juice (pepsin, chymosin, lipase); (2) ferments that appear in the stomach in carcinoma (proteolytic ferment); (3) ferments present owing to the admixture of bile, pancreatic juice and intestinal juice regurgitated through the duodenum

into the stomach (trypsin, amylolysin, lipase, etc.); and (4) ferments swallowed in the saliva (ptyalin, and peptid-splitting ferment).

(1) *The Ferments of the Gastric Secretion*

If a normal HCl content has been found, it is almost unnecessary to test for pepsin or the lab ferment, since the secretion of HCl and of these ferments run parallel, as a rule. When, however, there is marked diminution, or total absence, of HCl, the ferments should be tested for, since they are often present when HCl is absent.

Pepsin

Qualitative Test for Pepsin.—From 3 to 5 c.c. of filtered stomach contents are placed in each of two test tubes, together with a small piece of washed and dried fibrin, or a disc of coagulated egg albumen, say 5 mm. in diameter and 1.5 mm. thick. To one of the tubes, a few drops of 1 per cent HCl solution are added, and both tubes are placed in the thermostat at 37° C. If, after 6-12 hours, the fibrin or the albumen has not been dissolved in either of the tubes, pepsin, and pepsinogen, have been absent; if digestion has occurred only in the tube to which HCl has been added, then the stomach contents contained the ferment pepsin, or pepsinogen, but no free HCl. With a normal stomach juice, digestion is complete in both tubes in from one to two hours.

Fibrin, stained with carmine, may be used, if desired, for this test. The fluid grows ever more red as the digestion proceeds.

Quantitative Determinations of Pepsin.—Many tests have been devised, but two only will be described here.

1. *Mett's Test.*—Several small glass capillary tubes, 15 cm. long, are filled with egg albumen. It is best to use the albumen from several eggs mixed, in order to get more constant values. The capillaries are temporarily closed with bread crumbs, and are placed in a water-bath for five minutes at 95° C. to coagulate the protein, after which they are permanently closed with sealing-wax. Such tubes can be kept for a long time and used whenever desired.

On performing the test, a piece of the tube 2-4 cm. long, is filed off and placed in a test tube with filtered stomach contents and left for 24 hours in the thermostat at 37° C. to digest. The little column of coagulated albumen is attacked at both ends of the tube; at the end of 24 hours the length of the column digested is measured. In normal stomach juice, about 5-10 mm. will have been digested.

It is well to make control tests with the filtered stomach contents, diluted with 16 volumes of $\frac{N}{20}$ HCl (Nierenstein & Schiff).

2. *Edestin Method (Fuld).*—The protein of hemp can be purchased in the market as edestin (Merck). When dissolved in HCl, it is changed into edestan, which can be precipitated by NaCl; but when edestan is digested with pepsin, the digestion products are not precipitated by NaCl.

One prepares a solution of edestin 1:1,000 in dilute HCl of 30 acidity per cent (made by diluting 30 c.c. $\frac{N}{10}$ HCl with 70 c.c. distilled water). The filtered stomach contents are also diluted in the proportion of 1:10, or 1:20, with the same weak HCl solution, the 1:10 proportion being used if no free HCl is present, the 1:20 dilution when free HCl can be demonstrated in the stomach contents; the object of this is to carry on the digestion experiment with fairly constant acidity conditions.

Six test tubes are arranged in a row containing the following amounts of diluted stomach contents:

(1) (2) (3) (4) (5) (6)
0.1—0.16—0.25—0.4—0.64—1.0 cm.

To each test tube is added 2 c.c. of the edestin solution, and the tubes are allowed to stand in a rack at the room temperature for exactly 30 minutes. To each tube is now added 0.5 c.c. of NaCl solution (saturated in the cold), and one observes in which tubes a milky turbidity appears. In the first clear tube, all the protein has been digested.

For example, if 0.25 c.c. of a twenty-fold dilution of the filtered stomach contents are able to digest 2 c.c. of edestin solution, the pepsin value of the stomach juice is $\frac{0.25}{2\times20}=\frac{1}{160}$; and the juice is said to contain 160 pepsin units.

Normal stomach juice contains 100 pepsin units, all the edestin being digested in the 4th tube (0.4 c. cm.).

Chymosin or Rennin

This ferment, which coagulates milk, is a coagulase or casease. It is also called the lab ferment. It acts best when the juice is approximately neutral in reaction, thus differing from pepsin.

Qualitative Test for Chymosin.—To 10 c.c. of unboiled milk (amphoteric or neutral in reaction) in a test tube, a few drops (3 to 5) of filtered stomach contents are added and thoroughly mixed in, and the tube placed in the thermostat at 37° C. If rennin or chymosin be present, the milk will be coagulated within fifteen minutes or half an hour.

Qualitative Test for the Zymogen of Chymosin.—If coagulation do not occur with the above test, one makes another test, using 10 c.c. of fresh, neutral or amphoteric milk with 3 c.c. of a 5 per cent $CaCl_2$ solution, and adds 10 c.c. of filtered stomach contents first rendered alkaline with $\frac{N}{10}$ NaOH to inactivate any rennin present. If coagulation now occur the zymogen of the ferment, or the so-called prochymosin, is present (Riegel).

Methods for the quantitative estimation of the lab ferment have been devised but are as yet of no practical value.

Lipase

Tests for gastric lipase are, as yet, of no practical clinical value.

(2) *Ferments that Appear in the Stomach Contents in Carcinoma of the Stomach*

Though the diagnosis of carcinoma of the stomach depends mainly upon the physical signs, upon the secretory changes (absence of HCl), evidences of stasis and abnormal fermentations (lactic acid), upon the microscopical examination of bits of cancer tissue, and upon röntgenoscopy and serial röntgenography, many efforts have been made to find new methods that will help us to recognize incipient carcinoma of the stomach. These methods depend mainly upon the fact that certain ferments not present in the normal stomach juice appear, and can, by their effects, be recognized in the stomach contents in carcinoma cases. Among these tests we shall mention those of Salomon, Wolff and Junghans, Neubauer and Fischer, Grafe and Röhmer, and Abderhalden.

Salomon's Test for Carcinoma of the Stomach (Abnormal Protein Content).—This test is based upon the principle that an ulcerating surface in carcinoma constantly exudes serum into the stomach, so that protein other than that derived from the food enters the stomach.

To determine whether or not this is occurring, Salomon proceeds as follows: During the forenoon, the patient is given a fluid diet (milk, gruel, etc.), and, from 2 p. m. on, a diet that is not only fluid but is also free from protein (bouillon, coffee, tea, wine) in order to make the thorough cleansing of the stomach easy. At 9 p. m., the stomach is washed out most carefully with water until the washings are entirely clear; if there have been stagnation of food, this may be difficult and may require as much as 12-15 liters of water, a procedure often so fatiguing to the patient as to meet with serious objection.

The patient is warned to take nothing during the night. Next morning, 400 c.c. of physiological salt solution are poured through a stomach tube into the stomach, siphoned off again, then run in once more, to be siphoned off a second time, in order thoroughly to wash the internal surface of the stomach. The fluid thus obtained is examined chemically for total nitrogen by Kjeldahl's method, and for protein by Esbach's method.

In cases of carcinoma of the stomach, there is often a distinct flocculent precipitate of protein, amounting to 1/16-1/2 per cent (Esbach). The nitrogen content corresponds, on the average, to the amount of protein present (*i. e.*, 10-70 milligrams to 100 c.c. of fluid).

In chronic gastritis, gastroptosis and other non-carcinomatous diseases, protein is absent, except for a mere trace, and the nitrogen content does not exceed 16 milligrams of nitrogen to 100 c.c. of fluid. When the fluid gives a distinct flocculent turbidity, or when the nitrogen content exceeds 20 milligrams in 100 c.c. of the wash-water, the chronic gastric disease is, according to Salomon, very probably carcinoma.

The protein precipitate with Esbach appears to be more reliable than the nitrogen content.

E. H. Goodman has modified Salomon's test. He estimates the phosphates in the washings, a much simpler procedure than the determination of the N and the protein. He reports that normal persons show less than 10 mgs. per c.c., while in cancer the amount in greater.

Wolff and Junghans' Test for Dissolved Albumin in Stomach Contents as an Indication of Gastric Cancer.—When HCl and pepsin are absent from the stomach juice, one would expect no soluble albumin in the material aspirated one hour after a simple test breakfast. In simple achylia gastrica, this expectation is realized, but in cancer of the stomach with absence of free HCl, there is often as much soluble albumin as in a normal stomach. This is accounted for by Wolff and Junghans by (1) the action of ferments derived from the cancerous growth, (2) albumin secreted by the growth, and (3) diminished absorption due to secondary gastritis.

If free HCl is absent (Congo-paper test), six clean test tubes are set up, and with a calibrated pipet the following amounts of filtered stomach contents transferred to them:

1.0—0.5—0.25—0.1—0.05—0.05

The contents of each tube are next made up to 1.0 c.c. by adding distilled water.

To each tube, except the sixth, 9 c.c. of distilled water are added; to the sixth tube, 19 c.c. are added. The dilutions in the several tubes are now as follows: 1:10, 1:20, 1:40, 1:100, 1:200, and 1:400. The contents of the tubes are mixed thoroughly; then 10 c.c. are removed from the sixth tube, in order to equalize the amount in each.

On the surface of the fluid in each tube is now layered, very carefully and slowly, 1.0 c.c. of the following solution: Phosphotungstic acid 0.3, conc. HCl 1.0, alcohol (96 per cent) 20.0; distilled water to 200.0.

Each tube is examined at once for a white ring at the junction of the two liquids; if present in none, or in the first three only, the case is benign; if present up to and including the fourth, the diagnosis is doubtful, but cancer is probable; if in either of the last two tubes, malignancy is almost certain. F. W. Rolph has controlled the test and finds it valuable, provided certain sources of error, mentioned in his paper, are avoided.

Neubauer and Fischer's Test for Carcinoma of the Stomach (Glycyl-Tryptophan Test).—Through the studies of C. P. Emerson in Friedrich Müller's clinic, it was shown that the digestion of protein in the carcinomatous stomach goes to a stage beyond that in the normal stomach, presumably dependent upon the presence of an autolytic ferment. It was shown by Neubauer and Fischer, that such a ferment is present, and that it is capable of splitting a dipeptid (glycyltryptophan), unaffected by pepsin, into its two constituents, glycocoll and tryptophan; the free tryptophan can be recognized by means of a color test.

The test is applied to filtered stomach contents obtained after an ordinary test breakfast. The stomach contents must be free from blood (Weber's guaiac test), and from pancreatic juice and bile (layer test for bile with very dilute alcoholic solution of iodin and potassium iodid); it must yield no red color on the addition of bromin water. If all these tests are negative, the stomach juice may then be subjected to the test for the presence of the ferment.

The presence of preformed tryptophan in the stomach-contents is first ruled out (see Test, below). To 10 c. c. of gastric contents, one then adds 1 c. c. of the dipeptid, glycyltryptophan (Kalle & Co.); the surface of the mixture is covered with toluol (to prevent bacterial growth), and the tube kept at 37° C. for 24 hours. A sample is then transferred by pipet to a clean test tube and tested for

tryptophan; if found, the activity of a peptid-splitting ferment has been demonstrated.

In testing for tryptophan, to 2 c.c. of the fluid, a few drops of acetic acid (3 per cent) are added to acidify. Then bromin vapor is allowed to enter the test tube until it is visible as a slight brown tint in the upper part of the tube, or a little of the vapor may be transferred to it with a small pipet and rubber bulb, after which the tube is well shaken. If a rose color develops, free tryptophan is present. If negative at first, a little more bromin may be added and the shaking repeated. Excess of bromin is to be avoided. The same color will appear, in the presence of tryptophan, if a little aqueous solution of calcium chlorate (one-tenth saturated) be used instead of bromin vapor.

The test has been applied in a series of cases in the Johns Hopkins Hospital by Dr. John T. Sample, whose findings agree with those of other investigators in indicating that the test is of relatively little value in diagnosis. The fact that the test is sometimes positive in anacidity without carcinoma, may be due to the peptid-splitting enzyme of swallowed saliva, which is destroyed by feeble acid solutions (L. M. Warfield, A. H. Koelker).

Grafe and Röhmer's Test for Carcinoma of the Stomach (Hemolytic Test).—These authors found, in their extracts of the stomach contents in carcinoma cases, substances that hemolyze red blood corpuscles, and they have devised a cancer test based upon this observation. They assert that the hemolytic substance is oleic acid, set free in the diseased wall of the stomach either by an autolytic ferment of the carcinomatous tissue or by gastric lipase. Their test depends upon the estimation of the oleic-acid content of the stomach juice.

The stomach is thoroughly washed out in the early morning, as in Salomon's test. A test breakfast is then given and the oleic-acid content determined by a complicated chemical procedure (isolation of the fatty acids and quantitative determination with iodin and sodium-thiosulphate titration). For the details the original article may be consulted.

Abderhalden's Reaction as a Test for Cancer.—Abderhalden's method of testing for defensive ferments can be applied to the diagnosis of cancer. The general method has already been described in the section dealing with examination of the blood. In testing for cancer, an antigen made from carcinoma tissue is used.

Fifteen c.c. of blood are drawn from the patient fasting, the blood flowing through a needle directly into a sterile tube under aseptic precautions. The tube is placed in the thermostat for five hours, after which the clot and the corpuscles are carefully removed by centrifugalization. Three hydrometer tubes are sterilized. Into the first is placed 20 c.c. of chloroform water (1:200). A tested parchment thimble is inserted so that its surface comes into contact with the fluid. One gram of the antigen and 2 c.c. of serum are placed in the thimble. The other two hydrometer tubes are used as controls, the thimble in one of them receiving 2 c.c. of saline instead of serum, and that in the other, 2 c.c. of

saline with 2 c.c. of serum (without antigen). The three tubes are then carefully plugged and placed in the thermostat for 24 hours, at the end of which time the dialysates are tested with ninhydrin for protein bodies. If the serum contains the antiferment for cancer tissue, the dialysate in the first tube should yield a decided violet-blue color with ninhydrin. In this country, Bruère and Hardisty, in Martin's clinic in Montreal, have found the reaction helpful.

(3) *Ferments in Materials Regurgitated from the Duodenum into the Stomach*

These are described further on under examination of the duodenal contents.

Ferments Swallowed with the Saliva

Ptyalin is the principal ferment in the saliva and after the food is swallowed, its influence on starchy food continues until inhibited by HCl.

A **peptid-splitting ferment** swallowed with the saliva may be a disturbing factor when applying the glycyltryptophan test in suspected carcinoma (See above).

There is, as yet, no clinical advantage to be derived from testing the stomach contents for ferments derived from the saliva.

It is, however, desirable to know how starch digestion has proceeded in the stomach contents, and this can be judged of best by the test for erythrodextrin, for amidulin, and for achroödextrin.

Test for Starch Digestion.—To 5-10 c.c. of filtered stomach contents are added a few drops of Lugol's solution. A deep claret color indicates normal starch digestion (presence of erythrodextrin); a blue color indicates a faulty starch digestion (amidulin reaction); the failure of any color to appear indicates an active digestion of starch (transformation to achroödextrin).

Normal starch digestion speaks in favor of normal gastric secretion, while faulty starch digestion points to supersecretion and superacidity. An unusually good starch digestion points to subacidity.

The test for starch digestion is so easy to apply that it should not be omitted. In arranging a dietary the results of this test are often more helpful as a guide than the acid values determined by titration.

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iv. Interpretation of the Results of the Chemical Examination of Stomach Contents After Test Diets

We should keep clearly in mind the fact that it is not possible to be sure how much of the stomach contents we examine represents residue of the ingested diet and how much is secretion from the stomach itself. An increased amount or a decreased amount must be very cautiously interpreted since we have the factor of the motility of the stomach, on the one hand, and the factor of the secretion of the stomach, on the other, to consider.

Thus, for example, if the stomach contents are more strongly acid than normal, this hyperacidity might arise (1) from increased amount of gastric secretion (hypersecretion); (2) from qualitative change in the acid-strength of the fluid secreted; or (3) from increased motility of the stomach leading to early removal of the ingested fluid that ordinarily mixes with the secretion and diminishes the acidity (hypermotility).

Physiologists assert that, ordinarily, a qualitative change in the juice as secreted can be ruled out, so that in hyperacidity we have to differentiate mainly between hypersecretion and hypermotility.

The amount of HCl *normally* present, one hour after an Ewald, or a Dock, test breakfast is from 40 to 60 acidity degrees for the total acidity (= **A**), and from 20 to 40 acidity degrees for the free HCl (= **L**). This corresponds to a content of 0.15 to 0.2 per cent of HCl. Three to four hours after a Riegel test meal, the HCl content may amount to 0.3 or to 0.35 per cent. A total acidity that lies between 30 and 70 acidity degrees (= 0.11-0.26 per cent HCl) at the height of digestion may be considered normal, that is, a state of **euchlorhydria** exists.

In *abnormal secretion* we may find any one of the following conditions:

(1) Absence of secretion of HCl (**anacidity; achlorhydria**) may be met with in severe forms of gastritis, in fever, in the neuroses, in amyloid and atrophic diseases of the gastric mucous membrane. It is especially important, however, as an early sign of cancer of the stomach, this sign being present in from 85 to 90 per cent of all cases of gastric cancer.

If there be no gastric secretion at all, neither HCl nor ferments being produced, the condition is known as **achylia gastrica** (Einhorn). Such an achylia is most often due to an *organic disease of the gastric glands* (chronic catarrhal gastritis with atrophy; atrophy secondary to cancer, to pulmonary phthisis, or to pernicious anemia). In other cases, achylia gastrica is present without atrophy of the mucous membrane (*functional achylia*). Recently, the existence of the latter form has been disputed, and, though I am convinced that a functional achylia occasionally occurs, it is probably wise for the practitioner to attribute achylia gastrica, in each case, to an advanced organic disease of the gastric glands until he is able to prove that this is absent.

(2) Diminished amounts of HCl (**subacidity; hypochlorhydria**), the ferment secretion being still retained, is usually a sign of diminished secretion, of hypomotility, or of both, and is met with in anemia, in cachexia, in chronic gastric catarrh, and in some cases of cancer.

(3) Increase of HCl to an amount above 0.25 per cent (**superacidity; hyperchlorhydria**), may be due to hypersecretion, to hypermotility, or to both, and is often present in ulcer, in gall-stones, in colonic or ileal stasis, and in neurasthenic states; sometimes, it is temporarily present in the gastric crises of tabes.

(4) The stomach may secrete continuously, the juice being formed not only during digestion (as normally) but at other times also uninterruptedly, so that even the fasting stomach contains a fluid rich in HCl. This is the condition known as **gastrosuccorrhea,** or Reichmann's disease.

(5) The pepsin content usually, but not always, follows the HCl content of the stomach juice. A normal amount is called **eupepsia**; an increased amount, **hyperpepsia**; a diminished amount, **hypopepsia**; and entire absence, **anapepsia.**

When HCl is absent or diminished in amount, the proteins are badly digested, and fermentative changes, leading to the formation of lactic acid and other organic acids, are common; motility is disturbed and the stomach is often dilated.

When HCl is present in excess, the digestion of starches in the stomach is interfered with.

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v. On Testing the Digestive Functions of the Stomach Without the Use of the Stomach Tube

In some patients, conditions exist that contraindicate the use of the stomach tube. Moreover, now and then, a patient whose stomach should be examined by intubation declines to submit to the test. Certain methods are available for testing digestion without the use of the tube, but they are far from satisfactory. The three principal ones are: (1) Schmidt's connective-tissue test, (2) Sahli's desmoid test, and (3) Schwarz's fibroderm bismuth-capsule test.

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(1) *The Connective-tissue Test (Schmidt)*

This is based on the fact that when the gastric secretion is absent or greatly diminished, connective tissue masses appear in the stool after eating raw chopped meat. When the stomach is normal, a patient can digest 125 grams of chopped raw meat without residue in the stomach.

To perform the test, 100-125 grams of raw beef, put through a meat-chopping machine, are eaten by the patient. To make the meal more palatable, the surface can be slightly cooked if desired, as this makes only the outer layers of the mass of chopped meat digestible in pancreatic juice. Next day, the feces of the patient are examined for connective tissue. A portion is washed in a porcelain vessel, the connective-tissue masses being sought with a glass rod. Better still, the stool may be washed on a Boas' sieve.

It was believed, at first, that when the test is positive, free HCl is absent from the stomach juice. Later studies, however, show that, sometimes, a hypermotility of the stomach, or a diminution of the pepsin content with normal HCl content, may yield a positive result.

(2) *The Desmoid Test (Sahli)*

This test, also, is based on the principle that connective tissue is digested by the stomach juice, but not by the intestinal juice. Sahli uses catgut, which consists of reticulum (F. P. Mall), to tie up indicators in a small rubber bag, which is swallowed with the mid-day meal.

As an indicator, he uses a mixture of 0.05 gram methylene blue with 0.04 gram extract of licorice, and the same amount of powdered licorice. Before the desmoid pill is swallowed, one must make sure that it is water-tight; if thrown into a glass of water no coloring matter should come

out. If the urine within twenty hours after administration of the capsule turns a bluish green color, it is assumed that the stomach has secreted gastric juice in sufficient quantities to dissolve the catgut thread so that the contents of the capsule, on entering the intestine, can be absorbed and appear in the urine. If no color reaction appear in the urine, or if it appear later than normal, the result is negative, and this is a sign of disturbed gastric function in either the secretory or the motor power (H. Sahli).

Many control observations have been made by other clinicians and the view is generally held that *a positive result, if it occur within ten hours, is diagnostically valuable* as showing that the gastric secretion is fairly normal. M. Einhorn maintains, however, that raw catgut can be digested in the intestine and that therefore even the positive result of the test does not necessarily indicate a sufficient HCl secretion on the part of the stomach. T. R. Boggs' results indicate that the test has a definite place in clinical work.

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(3) *The Fibroderm Bismuth-capsule Test (Schwarz)*

A fibroderm bismuth-capsule is administered with an Ewald, or a Dock, test breakfast. The capsule is as large as the kernel of a hazel-nut, its cover consisting of so-called gold-beater's skin of definite thickness. This gold-beater's skin consists of crude connective tissue (reticulum) from cow's cecum. Inside the capsule is placed 4 grams pulverized, chemically pure, bismuth carbonate along with 0.25 gram pure neutral pepsin. The patient is examined fluoroscopically afterward.

The fibroderm capsule appears at first as a circular, sharply contoured, black area; but if the fibroderm capsule be dissolved by the stomach juice, the change in form of this shadow can be easily followed. The circular fleck is, on digestion of the capsule, transformed into a broad band, often convex below, where the bismuth comes into contact with the wall of the stomach. According to Schwarz, this change in shape of the bismuth shadow is, normally, always visible 2½ hours after administration. In hyperchlorhydria, it may occur as early as 2 hours, while in hypochlorhydria, it may not appear until after 4 or 4½ hours. Should the shape of the capsule remain unchanged at the end of 5 hours, anacidity of the stomach juice is assumed.

I have had no experience in the use of this test, but it would seem worthy of trial.

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(e) *The State of the Mucous Membranes of the Stomach as Inspected through the Gastroscope (Gastroscopy)*

Through the studies of Mikulicz, of Rosenheim, and, more recently, of Chevalier Jackson and of Elsner, direct inspection of the stomach through an instrument, similar in its mechanism to the cystoscope, has been made possible.

The simple stiff tube of Chevalier Jackson, bearing a lamp at its lower end, is one of the best instruments. One of the newer instruments is that of Loening and Stieda, which, through its combination of flexible and rigid tube, possesses especial advantages.

Carcinomata of the cardia and of the pylorus, round ulcers, and foreign bodies have been thus directly observed by gastroscopy.

Such gastroscopic methods, however, require special training and skill, are only rarely desirable, are not devoid of danger, and can scarcely be applied by the general practitioner. For these reasons, they will not be further discussed here.

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E. Special Examination of the Intestines and their Functions

Diseases of the intestines are even more common than those of the stomach. Irregularities of defecation, diarrhea, constipation, flatulence, etc., are met with quite frequently in practice. Owing to the great length of the intestinal tube (7-8 meters), the diagnosis of the exact site and nature of a disturbance may be very difficult.

The student approaching the study of intestinal diseases should

review the anatomy and physiology of the gastro-intestinal tract; such knowledge must here be taken for granted.

The small or thin intestine (*intestinum tenue*) includes (1) the *duodenum*, (2) the *jejunum*, or empty intestine, and (3) the *ileum* or twisted intestine. The large intestine (*intestinum crassum*) includes (1) the *cecum* or blind intestine, (2) the vermiform process, or *appendix*, (3) the *colon*, or great gut, and (4) the *rectum*, or straight gut.

The examination of this part of the body will be considered under the following headings: (1) special anamnesis; (2) determination of the form, size and position of the small and the large intestine; (3) special methods of examination of the rectum and sigmoid, including recto-romanoscopy; (4) examination of the functions of the intestines (motor, secretory, absorptive), and (5) the examination of the feces.

1. Special Anamnesis in Intestinal Cases

We inquire, especially, regarding (1) possible causes, and (2) certain suggestive symptoms.

In searching for **causes**, we ask about *preceding gastric affections* (chronic gastric catarrh, superacidity, subacidity, dyspeptic symptoms) and especially as to the existence of any organic disease of the stomach, which could be followed by perigastritis with adhesions or fistula.

Inquiry should also be made regarding *preceding infectious processes*, especially those involving the intestine (typhoid fever, dysentery, cholera, tuberculosis, syphilis), and certain *intoxications* (lead, mercury, arsenic, ptomain poisoning, etc.).

The *general body form* may be important (habitus enteroptoticus). The influence of *sex* should be kept in mind; in women, a history of many pregnancies, or of pelvic inflammatory disease, with or without adhesions, may be important; and in men, prostatic troubles may cause reflex intestinal disturbance. The bearing of *diseases elsewhere* in the body (liver, peritoneum, heart, spleen, kidneys) upon the intestinal functions should be remembered. The relation of intestinal disturbances to *disorders of internal secretion* (Basedow's disease), and to *diseases of the nervous system* (psychoneuroses and psychoses), is not to be forgotten.

On asking about **symptoms** of intestinal diseases, care should be taken to establish the exact *mode of onset*, and the *duration*, of the trouble complained of, and certain special *subjective symptoms* (pressure, fullness, distension, pain), and *objective symptoms* (irregular defecation, constipation, diarrhea, fever, tenesmus, hemorrhoids, peculiarities of the feces) should be noted.

When *pressure*, or *fullness*, are complained of in the whole abdomen, and these are not related to eating but seem to be related to defecation, and, especially, when they are complained of in the early morning before

breakfast, they are usually intestinal in origin. Fullness due to gastric disease is relieved by eructation, that due to intestinal disorders by the passage of flatus.

Pain of intestinal origin may be due to peritoneal irritation, or to violent contraction of the intestinal walls. The pain near McBurney's point in appendicitis is an example of the former, the pain of lead colic, and of spastic constipation, of the latter. Pains of intestinal origin are not directly related to eating. They are usually of short duration, lasting only a few minutes in ordinary colic, though sometimes for several hours (in lead colic), and are usually relieved by the passage of flatus. A common error is to confuse the pain of intestinal colic (spastic constipation) with pylorospasm, owing to failure to recall that pylorospasm is definitely related in time to food intake.

On asking the patient regarding *defecation* the following questions are useful: Do the bowels move regularly? How many times a day? Do you always go to stool at the same time, whether you feel inclined to, or not? Are the stools solid, or fluid? Are the stools bulky, or scanty? Have you noticed blood, or mucus, in the stools? Do you ever pass ribbonlike, or pencillike, stools, and, if so, are the feces covered with mucus? Are the stools frothy? Is there any pain at stool? Have you noticed worms, or anything peculiar, in the feces? Have you had pain in the abdomen, and, if so, is it relieved by the passage of wind? Have you suffered from hemorrhoids (piles)?

2. Determination of the Form, Size and Position of the Small and Large Intestines

Here we make use of (a) inspection, (b) palpation, (c) percussion, especially after distension of the large intestine with gas or fluid, and (d) x-ray examinations.

Through the studies of F. P. Mall, we know that, normally, the intestinal loops occupy definite positions in the abdomen. The newer methods of palpation of the abdomen, and, above all, x-ray examinations of the intestine filled with bismuth, have taught us much regarding the position and configuration of the whole intestine, and, especially, of the different parts of the large intestine, of the first portion of the duodenum, and of the lower ileum.

(*a*) *Inspection of the Intestines*

This has already been referred to under the general methods of examining the abdomen. It is only rarely that inspection gives us information of importance regarding the form, size and position of the intestine. Occasionally, when the abdominal walls are very thin, or the intestine

is markedly contracted, the contours of certain portions of the intestine are recognizable (so-called "abdominal patterns" of Wyllie).

Visible peristalsis of the intestine may sometimes be seen in emaciated persons when the intestines are normal. In intestinal stenosis, marked *visible peristalsis, always arrested at a definite spot,* may be of importance in localizing diagnosis.

(*b*) *Palpation of the Intestines*

The general methods of palpating the abdomen have already been described. Here we shall call attention to some special points of importance. With two exceptions, individual loops of the *small intestine* are not recognizable on palpation. The exceptions are, (1) the cecal part of the ileum (*pars cecalis ilei*), that is, the terminal portion of the ileum, which rises out of the pelvis to end, at the valve of the colon (ileocecal valve), in the cecum, and (2) the horizontal part of the third portion of the duodenum (*pars horizontalis* [*inferior*] *duodeni*). The latter can, occasionally, in emaciated patients with visceroptosis, be felt as a cord, lying in the depth, one or two finger's breadths above the navel, sometimes on the right of the middle line only. In contrast to the transverse colon, it can be followed by palpation for only a short distance, is only slightly mobile, does not gurgle, and lies directly over the aorta, the pulsation of which it transmits to the palpating hand. Occasionally, three transverse structures, more or less parallel to one another, can be made out, (1) above, the palpable pylorus, (2) in the middle, the portion of the duodenum mentioned, and (3) below, the transverse colon.

No attempt should be made to palpate the cecal portion of the ileum until after the exact position of the cecum and the different parts of the colon have first been determined.

When palpating the *large intestine*, the palpatory movements should be made perpendicular to the axis of the portion of intestine under study, the fingers gliding over the depth of the abdominal cavity without separation of them from the anterior abdominal wall (Glénard's *procédé du glissement;* Hausmann's *Gleitpalpation*). By such a mode of movement, the sensation of a cylindrical body can be most distinctly and quickly secured.

One outlines (1) the cecum, together with the lower part of the ascending colon, (2) the transverse colon, and (3) the sigmoid colon (together with the lower part of the descending colon). After these have been carefully studied, the palpation may be extended to the cecal portion of the ileum, and, last of all, to the vermiform process or appendix.

Palpation of the Cecum and Ascending Colon.—Seated at the right of the patient, one palpates with the right hand, from above downward and from the middle line lateralward, the fingers being held at right angles to the long axis of

the bowel. The palpation is begun on a line connecting the umbilicus with the anterior superior iliac spine. It will be favored if the patient will keep up deep abdominal breathing, and if the examiner squeeze the right flank between the thumb and fingers of his left hand, thus holding the cecum in the iliac fossa against the palpating right hand.

Palpation of the Transverse Colon.—One palpates with both hands, one on each side of the umbilicus and about at its level, the tips of the fingers being held perpendicular to the normal course of the transverse colon. Palpation here is favored when the patient voluntarily retracts the abdominal wall slightly, so as to bring the transverse colon nearer the back of the abdominal cavity, against which it can be pressed. If the transverse colon be not felt in this way, the finger tips may be kept firmly pressed inward while the patient takes a deep breath. On testing spot after spot, one may be found beneath which the transverse colon passes. Sometimes, it is possible to feel the right, or the left, flexure of the colon in this way.

Palpation of the Sigmoid Colon and Lower Part of Descending Colon.—This portion of the large intestine is by far the easiest to palpate; it can be felt in nearly all persons. One palpates with the fingers of the right hand, along a line drawn from the umbilicus to the left anterior superior iliac spine.

Palpation of the Cecal Portion of the Ileum.—The patient is told to hold the extended right lower extremity about a foot high, so as to contract the ileopsoas muscle and bring it nearer the anterior abdominal wall.

The junction of the ileum with the cecum (position of the valvula coli, or cecal valve) corresponds to *McBurney's point* (4-5 cm. from the right iliac spine on the line connecting the latter with the umbilicus, that is, at about the junction of the lateral and the middle third of the spino-umbilical line). It was formerly believed that this point corresponds to the position of the vermiform process or appendix, but, as Arthur Keith has shown, the latter lies, as a rule, from 3-5 cm. lower, at *Lenzmann's point* (on the linea bis-iliaca, 6 cm. medialward from the right anterior superior iliac spine), or at *Lanz's point* (on the linea bis-iliaca at the junction of the right with the middle third of this line).

On palpating the vermiform process, or appendix, one uses the index finger, holding its radial margin at right angles to the course of the ileopsoas, and, passing along the latter, uses pressure enough to feel the sharp, stiff, margin of the muscle until one comes to the appendix.

Results of Intestinal Palpation.—The **cecum** is felt as a tube 4-5 cm. thick, rounded off at its lowest extremity, gurgling on pressure, and movable in the transverse direction. It can be so felt in about two-thirds of the cases. Sometimes, it is broader and more tense, pear-shaped, more mobile (*cecum mobile*), sensitive to pressure, with loud gurgles (distended cecum); or it may be met with as a tube of normal diameter, but of firmer consistence than normal, tender on pressure and non-gurgling (the so-called *boudin cécal* of perityphlitis); or, finally, it may occur, as a hard, cylindrical, non-gurgling cord of small caliber (*"pipe-stem" cecum*).

The **transverse colon** is often very difficult to palpate, though it may be felt as a soft tube 3-4 cm. thick, yielding a feeble, gurgling, sound, on pressure. It is more easily displaceable upward than downward. In order to be sure that a transverse cylinder is the colon, it must be felt for at least four fingers' breadths on each side of the middle line, and it must agree in caliber, in consistence, and in gurgling, with what one finds on palpating the large intestine elsewhere. In spastic constipation, the transverse colon and the sigmoid may be of small caliber, firm and contracted, while the cecum is distended. In ptosis of the transverse colon, this portion may form a **V** or a **U**, in which event, palpation may reveal an **M**-

shaped figure with an ascending and descending tube more or less close to one another, in each lateral half of the abdomen. Thus, on the right side, the cecum and the descending part of the transverse colon may be felt, and on the left, the ascending part of the transverse colon and the sigmoid. In recognizing these parts, the rounded lower end of the cecum, on the one hand, and the termination of the sigmoid in the pelvis, on the other, should be kept in mind.

As has been said, the **colon sigmoideum** (*or S-romanum*) is usually very easy to palpate as a moderately firm, cylindrical cord, in the left iliac fossa, yielding slight crepitation on pressure. Passing downward, it vanishes in the pelvis; it is susceptible to considerable transverse displacement. It varies in size and consistence. It can often be felt when the transverse colon is not palpable, while the reverse is never true, except in stenosis of the splenic flexure of the colon (Sacconaghi).

Occasionally, the sigmoid is unusually curved, and has such a long mesocolon that it may cross the middle line and even extend over as far as the cecum, or upward as far as the liver, making an O-shaped cushion demonstrable on palpation and percussion above the symphysis pubis (controlled by blowing up the colon, or, by injecting fluid per rectum).

The **cecal portion of the ileum**, when palpable, is felt as a tube the size of the little finger, sometimes relaxed and nearly empty, sometimes tense and filled with feces. On pressure, a slight rumbling sound can be heard. Its shape and consistence frequently change under examination, a point of great importance in distinguishing it, when strongly contracted, from the vermiform appendix. It is most often palpable in typhoid fever, and may then be painful, thickened and nodular.

The **vermiform process or appendix** is palpable in a certain proportion of cases, variously estimated from one-fifth to one-half. Even then, much skill may be required. It usually lies transversely, varying in thickness (averaging that of a goose quill). When tender, the pain often radiates out into the abdomen, being sometimes most marked at the umbilicus. No gurgling is producible in it, nor can outspoken changes in size, or consistence, be detected (contrast with cecal portion of ileum).

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(*c*) *Percussion of the Intestine Before and After Distension with Gas or Fluid*

Percussion of the abdomen in general has already been described (See General Examination of the Abdomen). It is sometimes advantageous, however, to distend the intestine with air, or with water, and then to percuss.

Distension with Air.—A soft rectal tube is passed and air blown in by a bulb, under gentle pressure. The distension soon becomes visible, and, on auscultation in the left iliac fossa, the entering air can be heard. Data regarding the position of the large intestine, the existence of a stenosis, or the localization of an

abdominal tumor, may thus be obtained. If there be a stenosis of the colon, only that portion of the large intestine rectalward from the stenosis becomes distended.

Distension with Water.—The fluid is allowed to flow in through a funnel attached to a soft rectal tube. The method is sometimes helpful in locating the position of a stenosis, or of an abdominal tumor by inspection; on percussion, too, the position of the large intestine can be well outlined. Distension of the large intestine with water is sometimes combined with gaseous distension of the stomach, in the diagnosis of abdominal tumors; for intestinal tumors become displaced in the direction of the portion of the intestine in which they arise. The amount of fluid that can be poured in to the colon may give a clue as to the site of a stenosis. If a patient cannot receive more than one liter, the obstruction must be in the lower part of the large intestine.

Great care should be used in injecting either air or water, as the procedures are not devoid of danger (perforation).

(*d*) *Examination of the Size, Form, and Position of the Intestines*

Studies by x-rays of the passage of contrast materials (bismuth, barium, thorium) through the intestines are of great importance in establishing the position of the tube, the size of its lumen, and its motility. The data obtainable are as yet, however, much more important for the large intestine than for the small bowel, though information of great value concerning the duodenal cap and the lower ileum can now be obtained by röntgenography. The bismuth meal, after leaving the stomach, passes so rapidly through the pars descendens and the pars inferior of the duodenum, and through the jejunum and the upper ileum, that conclusions regarding the position of the single loops (unless there be a stenosis) are difficult to draw. By röntgenoscopy, by serial röntgenography, and by röntgenocinematography, even these portions of the gut are accessible, also, to x-ray examinations.

The large intestine can be clearly outlined in its different parts by x-ray examination, either by photographs taken six, nine, twelve, twenty-six, thirty-two and fifty hours after a contrast meal, or, by röntgenoscopy or röntgenography, after the administration of a contrast enema. Since it is usually desirable to know the condition of the stomach as well as that of the intestine, studies made by means of the contrast meal are usually undertaken first, and the bismuth or barium clyster given subsequently.

Moreover, the *contrast meal* is necessary for (1) the study of the duodenum, (2) the study of obstructions in the course of the small intestine, (3) the study of the position of the different parts of the large intestine, and (4) the study of the motor function of the colon; while the *contrast clyster* is necessary for (1) the study of marked obstructions of the large bowel, due to cancer, other tumors, constricting bands, adhesions, etc., and (2) the testing of the function of the valvula coli, or so-called ileocolic valve.

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[Note.—See also references under Roentgenology of the Stomach.]

i. Administration of the Contrast Meal and Its Normal Journey through the Digestive Tract

No purgative should be given on the day immediately preceding the examination. The contrast meal should be given either in association with, or as a substitute for, one of the ordinary meals, in order that the regular rhythm of meals will not be disturbed. It is now customary to use the barium-sulphate meal (see Röntgenology of the Stomach), though it should be remembered that this passes through the stomach somewhat more quickly than a bismuth meal. Thus after a barium meal, the stomach, if normal, should empty itself within 4½ hours and the head of the opaque barium column should, by that time, have reached the cecum. By the 8th hour, or, at latest, by the 10th hour, the whole barium meal should have passed into the large intestine, and by this time the head of the contrast column should have arrived at the middle of the transverse colon. From 9 to 16 hours after the ingestion of the barium meal, the head of the contrast column should get as far as the colon descendens, and by the 36th hour the colon should be practically free from the contrast substance. Röntgenoscopy and röntgenography of the colon are best undertaken at the 9th, the 26th, the 32d and the 50th hour after ingestion of the meal.

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ii. Administration of the Contrast Clyster

Various formulae have been employed in the preparation of the contrast clyster. Any one of the following may be used:

Case's formula.—To 2½ drams of gum tragacanth, add about 1 ounce of alcohol. Shake well. Add 20 ounces of warm water, and shake. Add 3 ounces of barium sulphate, then 20 ounces of water, shaking well each time. The mixture should be made up fresh shortly before use.

Haenisch's formula.—Bolus alba 300 g., bismuth subcarbonate 75 g., water to 1 *l.*

Holzknecht and Singer's formula.—To 1 *l* boiling water, add a suspension of three tablespoonfuls of finest potato starch in 0.75 *l* cold water; boil, and stir in 160 *g.* barium sulphate and 250 *c.c.* hot water. Boil for 5 minutes; then cool down to 44.5° C. (=112° F.). Thus prepared, the material may be preserved for several days in the ice-box, and be warmed up when required for use.

Jaugeas and Friedel's formula.—These authors use a paste for the study of the rectum and the colon sigmoideum. To a mixture of equal parts of vaselin and oil, they add an equal amount of barium sulphate, or of bismuth carbonate, incorporating thoroughly. The paste is injected with a syringe, one liter being sufficient to reach the flexura coli sinistra.

The contrast enema is best *introduced under röntgenoscopic control,* as advised by Haenisch. The large intestine should be empty, either from the administration of castor oil the night before, or from an effective soapsuds enema, given at least two hours before the contrast clyster is introduced.

The patient lies *supine upon the trochoscope* (or horizontal röntgenoscopic table). The contrast material, prepared according to one of the formulae given above, and warmed to body temperature or a little higher (100° F.), is placed in a container about 1 meter above the patient, and allowed to flow through an ordinary enema-tube into the bowel. The tip of the tube need not be inserted for a greater distance than 2 or 3 inches. By röntgenoscopy, the progress of the clyster, inch by inch, should be observed. During inflow, manipulation with the wooden spoon may be helpful. It is the observation of the filling of the colon at every stage that permits one accurately to determine the presence or absence of pathological conditions of the lumen. After the examination, if desired, the emptying of the colon can also be observed by röntgenoscopy, the container being lowered and the contrast material allowed to return into it by gravity; sometimes, additional information is thus gained regarding the precise site of an obstruction. If features of special interest are observed röntgenoscopically, they may be permanently recorded by röntgenography. If the filled vermiform process is to be photographed, it must first be found by röntgenoscopy, after which the cecum or other contrast-filled bowel must be held out of the way by the wooden spoon.

When incompetency of the valvula coli and ileal stasis are suspected, the röntgenogram should be made with the patient lying prone, plate anterior, rather than lying supine, plate anterior (J. T. Case), for in the latter position, the "saddling" of the ileum over the iliopectineal line may lead to confusion. A pair of stereo-röntgenograms may be helpful, especially when it is desired to study the pelvic colon carefully.

iii. The Form, Size and Position of the Duodenum, as Determined Röntgenologically

Thanks, especially, to the studies of the röntgenologists, our knowledge of the appearance of the duodenum, and especially of its first portion, the so-called **duodenal cap** (called by Cole the *pilleus ventriculi* because he regards it as

really belonging to the stomach rather than to the duodenum, but known to anatomists as the *pars superior duodeni*) has, in recent years, made great progress.

The *normal shadow* of this cap has been carefully studied and is now familiar to every röntgenologist, so that slight variations from the normal are easily recognizable. The dimensions of the cap, like those of the stomach, depend partly upon its distension during different stages of digestion, different phases of the cycle, and different stages of duodenal peristalsis. The cap appears to be a reservoir where, as Cole puts it, the "finishing touches" of gastric digestion may be applied to the small amount of chyme thus isolated from the bulk of food in the stomach. The cap is separated from the stomach by a clear space $\frac{1}{8}$ to $\frac{1}{4}$ inch wide, which indicates the position of the M. sphincter pylori. The lumen of the sphincter is normally centrally located and is, at first, about $\frac{1}{8}$ inch in diameter during systole, though it becomes twice as large later, owing to gradual relaxation. The cap is emptied periodically by a propulsive peristalsis, which advances the chyme through the pars descendens and the pars inferior duodeni in characteristic *fingerlike masses* first described by Holzknecht.

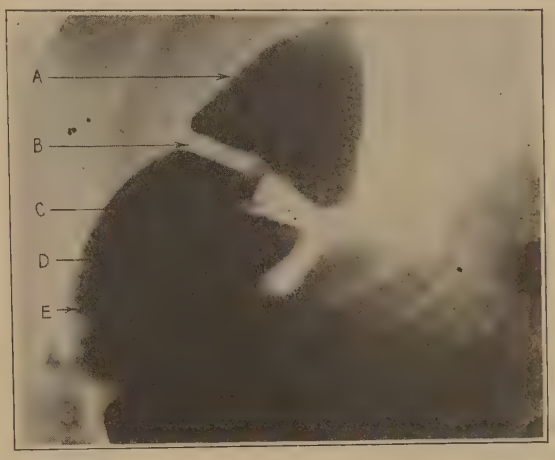

Fig. 344.—Normal Duodenal Cap; (A) Cap; (B) Sphincter; (C) Lumen of Sphincter; (D) Congenital Fold; (E) Terminal Wave. (After L. G. Cole, The Lancet.)

Fig. 345.—Ulcer of Duodenal Cap: (A) Cap; (B) Sphincter; (C) Terminal Wave; (D) Descending Duodenum. (After L. G. Cole, The Lancet.)

The **pars descendens duodeni**, rich in circular folds, descends at an acute angle from the top of the cap to join the horizontal portion of the **pars inferior**, the two fitting around the head of the pancreas and being fixed in position. In röntgenograms, this portion of the duodenum, if filled or partly filled, can be identified by its shape, its position and the ringlike appearance of its circular contractions. On röntgenoscopy, the motor phenomena are characteristic (see Motility).

Normally, the duodenal cap, when at rest and full of contrast material, is well filled out and shows everywhere smooth edges.

Abnormal shadows of the duodenal cap may be due to duodenal ulcer, to penetration, or perforation, of a chronic ulcer, to cicatricial contraction, to stenosis, to pressure from the outside from extraduodenal tumors, or to adhesions between the duodenum and the gall-bladder (or between the duodenum and the pancreas). Cole maintains that abnormal findings in the cap-shadow are of extraordinary value for diagnosis, if the röntgenograms of a large series are studied individually and collectively and are matched over each other, or reproduced cinematographically. He states, however, that attempts to apply these diagnostic points to a study of two or three, or even a dozen, röntgenograms will only lead to errors and reflect discredit upon the method. Among the diagnostic points thus far available may be mentioned the following:

(1) The *induration of an ulcer* may project into the lumen of the cap, causing a displacement of the contrast material like a finger-print in a ball of putty. Such a *filling-defect* may be very small, a mere dent on one side of the cap, or it may be very large, so as to distort the lumen of the cap beyond recognition.

(2) A duodenal ulcer may be viewed sometimes in profile, the *indurated edges* projecting into the lumen, and the *crater* of the ulcer being filled with bismuth. Retention in such a "bullet-hole" pocket must be carefully distinguished from "pouching," and from normal accumulations in the cap.

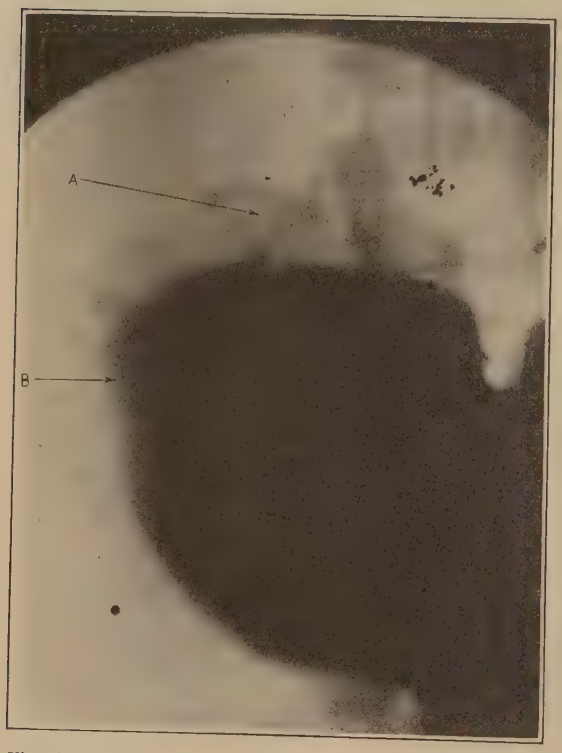

Fig. 346.—Ulcer of the Duodenal Cap with Pyloric Obstruction and Prognathian Dilatation: (A) Complete Destruction of Cap; (B) Prognathian Dilatation of the Stomach from Pyloric Obstruction. (After L. G. Cole, The Lancet.)

(3) The *puckering from cicatricial contraction* may yield a deformity as marked as that due to induration; it may be hard to tell whether a deformity is due to induration or to adhesions or to both. Often, besides the deformity of the cap, a band of adhesions can be seen passing over on the gastric side of the pyloric sphincter, so as to distort the contour of the extreme pyloric end of the stomach.

(4) *Pouching* due to a portion of the duodenal wall being separated from the rest by being pinched away from it (Moynihan) is represented, röntgenologically, as a distension of the uninvolved portion of the cap. Such pouches may sometimes be mistaken for bismuth flecks in the craters of ulcers.

(5) Very slight permanent irregularities of the cap of constant shape, much smaller than the preceding lesions, may be due to *healed ulcers* or *scars*.

(6) Distortions of the cap, similar to those due to ulcer, may be due to *spasm*

(See Disturbances of Motility), but are shown to be spasm and not ulcer, since, sooner or later in the series, a röntgenogram showing a normal form of cap and sphincter will be met with.

(7) In *gall-bladder infection with adhesions to the cap,* the picture may closely resemble that of distortion from duodenal ulcer, but, as a rule, there is a more extensive involvement of the pylorus and the cap; the stomach is drawn over to the right (*hepato-fixation*), and there is *angulation of the cap.* There is no evidence of a localized area of induration in the cap, and its lumen is less frequently obstructed. In either duodenal ulcer or gall-bladder adhesions, surgical therapy is usually indicated, so that differentiation is less essential than it would otherwise be.

(8) Adhesions following a *periduodenitis,* secondary to duodenal ulcer, may involve and obstruct the pars inferior duodeni and cause an unusual dilatation of the whole duodenum behind it (*sausage-shaped duodenum* of Holzknecht).

(9) A more frequent cause of the sausage-shaped duodenum is chronic obstruction in the third portion of the duodenum by the blood vessels in the root of the mesentery (*angiomesenteric ileus*), the lesion so well described by Codman. An ulcer on the posterior wall of the stomach with *perigastritis,* may also involve the duodenojejunal junction and cause similar obstruction.

According to Cole, the pathology of the duodenum can be very accurately diagnosed by means of serial röntgenography; the results are as accurate as in the röntgenological diagnosis of renal or ureteral calculus. His views are supported by George of Boston. The procedure is elaborate and expensive, but undoubtedly warranted, if the results are as good as these authors assert.

It seems to me exceedingly important that *clinical and röntgenological studies should control one another* in the diagnosis of disease in this region. Neither the purely clinical, nor the purely röntgenological studies, should be trusted by themselves, but, taken together, the best judgment possible in the circumstances should be formed before a decision regarding therapy is reached.

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[Note.—For other references, see Duodenal Ulcer.]

iv. The Form, Size and Position of the Jejunum and Ileum as Determined Röntgenologically

Leaving the duodenum, the contrast material enters the jejunum in the left upper quadrant of the abdomen and is here broken up into fine particles appearing in röntgenograms as flocculi. This *flocculent appearance* is characteristic of the jejunum and distinguishes it from the rest of the small intestine.

On entering the **ileum**, the contrast material normally forms into so-called *coagulated masses*, and on reaching the lower portion of the ileum the latter collect into *long, wormlike coils*, which, near the cecum, may so fill the lumen that several continuous gyri of the lumen can be identified in stereoröntgenograms. Cole gives as criteria for the röntgenographic recognition of the ileum (1) its location in the right lower quadrant of the abdomen, (2) the coagulated appearance of the contents in its upper portion, and (3) the well-defined wormlike coils in its lower portion.

These varied appearances in different parts of the small bowel depend partly

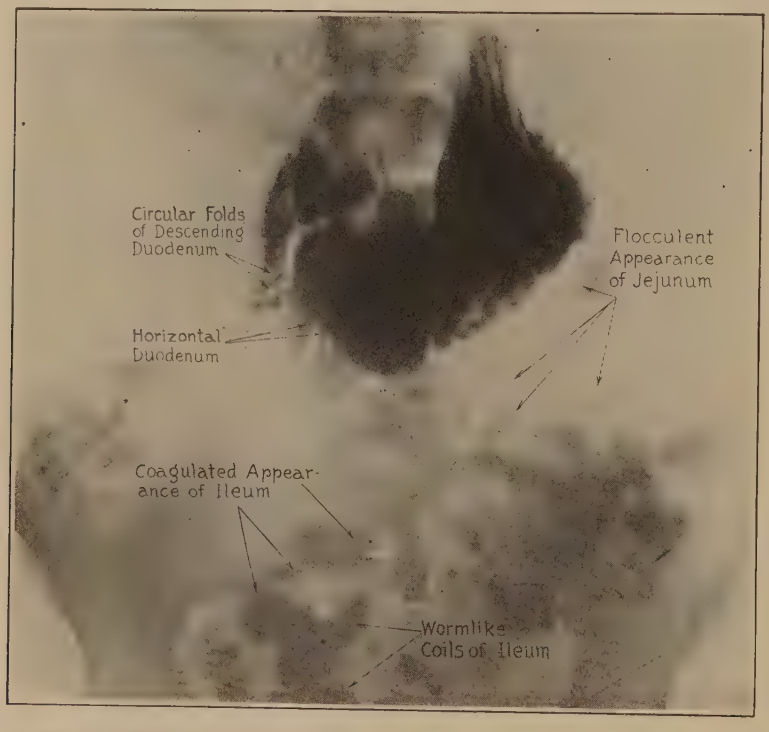

Fig. 347.—Usual Röntgenographical Appearance of the Duodenal Cap, the Descending Duodenum, the Jejunum, and the Ileum. (After L. G. Cole, Am. J. Med. Sc.)

upon the consistency of the contents, partly upon the motility characteristic of each region, for when the valvula coli is incompetent and a contrast clyster passes through it into the ileum and jejunum, the features above mentioned as characteristic after a contrast meal are not present (Cole).

Ileal Stasis.—In the fore-front of clinical interest during recent years, especially among surgeons, has been the question of **intestinal stasis.** Attention, at first, was directed by Lane to **colonic stasis.** Subsequently, his interest centered upon **ileal stasis,** which is now generally believed to be the much more important of the two. Though Lane's teaching regarding (1) kinks in the ileum and (2) the importance of short-circuiting the intestine and colectomy, are now being generally abandoned, and though his ideas concerning the relation of intestinal stasis to pathological processes elsewhere in the body (cancer, tuberculosis, cystic degeneration of the breasts, nephritis, senility, insanity, loss of sexual power, etc.) are con-

sidered, by more conservative physicians, as decidedly excessive, still great credit is due to the London surgeon for having emphasized the danger of continued stasis in the *prima via* and the necessity of doing something, medical or surgical, to relieve it.

For the elucidation of the subject of intestinal stasis, and especially of ileal stasis, röntgenology has recently proved to be of great service. It seems now that, while ileal stasis may, in some instances, depend upon adhesions or kinkings of the terminal ileum (including Lane's kink), and that spasm of the muscle of the terminal portion of the ileum itself (the so-called ileocecal sphincteric mechanism

Fig. 348.—Röntgenogram after a Contrast Meal Revealing a Lane's Kink. Proved by Operation. (After L. G. Cole, Am. J. Med. Sc.)

studied by A. Keith) may be another causative factor, the most common cause of ileal stasis is incompetency of the valvula coli (J. T. Case). In considering ileal stasis, it should not be forgotten that in 98 per cent of all cases examined by a contrast meal, bismuth is present in the ileum 7 hours after ingestion. It is best not to reckon ileal stasis from the time of ingestion to that of the appearance of the first bismuth in the cecum alone, but also to check up by noting the time that elapses between the complete evacuation of the stomach and the evacuation of the ileum, since ileal stasis may cause a functional gastric retention (Cole).

Kinks in the terminal portion of the ileum may occur either with, or without, mobile cecum. Jordan bases his diagnosis of kink of the terminal portion of the ileum **(Lane's kink)** on immobility of this region on palpation during röntgenoscopic examination, with, or without, signs of ileal stasis. Cole asserts that kinks here, with dilatation of the proximal ileum, are sometimes undoubtedly demon-

strable. If present in marked form, he regards the kink as an indication for surgical relief, but he asserts that ileal kinks are relatively rare, and, like Case, is of the opinion that ileal stasis is not caused solely, or even largely, by kinks of the terminal portion of the ileum. Ileal stasis not due to a kink may be aggravated by operations to release a kink.

v. The Form, Size and Position of the Cecum, Ileocecal Junction, Vermiform Process or Appendix, and Ascending Colon, as Determined Röntgenologically

The **cecum** and **colon ascendens** are easily recognizable by their position in the right side of the abdomen and their large size. The blind head of the cecum has a characteristic shape, and the junction of the ascending colon with the transverse colon is usually evidenced by a sharp bend at the *flexura coli dextra.*

A mobile cecum (*cecum mobile*) is easily recognized by palpation with the protected hand, or the wooden spoon, during the röntgenoscopic examination. Formerly, this mobile cecum was held to be a pathological condition and thought to be responsible for symptoms. Today, the mobile cecum is considered relatively unimportant, a cecum fixed by adhesions much more often giving rise to symptoms. The operation for fixing the mobile, atonic, cecum, introduced by Wilms, has been given up.

A *fixed cecum* or ascending colon, or an ascending *colon constricted by bands* (Jackson, Eastman, Hertzler) can be well made out by röntgenoscopy. The site of adhesions, veils, and membranes, is ascertainable, as well as their accessibility to surgical interference. Among the important signs are (1) drawing up of the cecum, (2) irregular filling-defects in the colon, and (3) especially the "double-barrel shotgun" appearance of the colon ascendens and the beginning of the colon transversum (George). Cole believes that colonic stasis is the most common cause of ileal stasis and that overdistension of the cecum and colon ascendens constitutes a large proportion of colonic stasis; on the other hand, Case is of the opinion that the ascending colon is less often the site of pericolonic adhesions than is the pelvic colon at the iliopelvic junction.

When examining a patient, röntgenoscopically, for colonic abnormalities, the *horizontal position on the trochoscope* is the one to be adopted. The examiner and the patient should be thoroughly *protected.* The exposure times should not be too prolonged, the foot-switch being made use of, so that the illumination may, from time to time, be interrupted. In making use of *guided palpation,* it is better to use the wooden spoon whenever possible, instead of the protected hand (Pfahler, Case, Skinner).

In testing for incompetency of the **valvula coli** or ileocecal valve, the following method is advised by J. T. Case: "The patient should lie supine on the horizontal fluoroscopic table. It is not necessary to introduce the rectal point, or colon tube, more than 1 or 2 inches. The container should be placed not higher than two feet above the patient and the barium or bismuth enema allowed to flow in by gravity, the course of the bismuth column being watched fluoroscopically. Ordinarily 1,200 c.c. of the barium enema at 100° F. will suffice to fill the colon. It is important that a uniform technic be followed. I insist on seeing, by means of the fluoroscope, that the cecum is well filled. Massage of the abdomen over the shadow of the cecum is practiced in the antiperistaltic direction. Still further to insure complete filling of the cecum, the patient is sometimes asked to lie on the right side for ten or fifteen minutes after the injection of bismuth, and a second examination is made when the patient returns to the table after evacuating the colon. The röntgenograms are made with the patient lying prone, plate anterior,

rather than lying supine, plate anterior. In the latter position "saddling" of the ileum over the ileopectineal line may lead to confusion. In marked cases of ileocolic valve insufficiency, however, there is never any difficulty in recognizing the terminal ileum."

The technical röntgenological examination of the **processus vermiformis**, or **appendix**, has now been well worked out (J. T. Case, A. George). Case asserts that the appendix may be shown in about 50 per cent of the cases by milking the bismuth into its lumen, while George maintains that he can reveal the appendix in 8 cases out of 10 if it has not been removed. When it is possible to fill it, its size, shape and position can be accurately determined, as well as the presence, or absence, of areas of constriction or permanent kinks, and whether or not it is adherent to adjoining viscera. After a contrast meal the appendix, if patent, usually fills spontaneously shortly after the cecum begins to fill (at about the sixth hour). For röntgenoscopic study of the appendix, a time should be chosen that will leave a sufficient interval after the contrast meal for the ileum to become empty; otherwise a thin shadow due to contrast material remaining in the terminal ileum may be taken for the appendix.

Case emphasizes (1) the necessity of examining the patient in the horizontal position, the fluoroscopic screen over the abdomen, and the tube underneath the table, and (2) the necessity of palpating the abdomen under the screen with the gloved hand, or, preferably, with the wooden spoon.

To make a röntgenographic record of the shadow of the bismuth-filled appendix is often very difficult. Case advises finding the appendix röntgenoscopically and then making the röntgenogram, holding the cecum or other shadow-yielding bowel out of the way by means of the wooden palpatorium.

About 1 in 3 patients showing gastrointestinal symptoms have a patent appendix. If an appendix fills but empties itself promptly, it need not be considered pathological. But if an appendix remain visible for more than one or two days following the contrast meal, it is to be regarded as a dangerous appendix owing to its poor drainage. An appendix may remain visible for even weeks after the rest of the bowel has been emptied. Appendicitis sometimes develops after an x-ray examination, but there is no more danger from a bismuth meal than from the administration of bismuth for diarrhea, since Case has shown that bismuth so given therapeutically often appears in the appendix, and in one instance was found on the 19th day after the last dose of bismuth.

The *normal appendix* empties itself quickly after the bismuth has entered it, is free from tenderness on guided palpation, is, together with the cecum freely movable, and shows no kinks or constrictions. If an *appendix cannot be*

Fig. 349.—Chronic Adhesions in the Lower Right Quadrant, Due to Appendicitis. Note How the Pylorus Has Been Pulled Down. (By Courtesy of Dr. Baetjer and Dr. Waters, X-ray Dept. J. H. H.)

made visible, this may be due to (1) a chronic obliterative process, (2) a kinking near the cecal end, (3) an infiltration and swelling, or (4) a retrocecal position with adhesions of the cecum preventing its being made visible by guided palpation.

It is rarely possible to fill the appendix by means of a bismuth enema. *Stones* and other *foreign bodies in the appendix* have been demonstrated röntgenoscopically (Fittig and Weisflog, Case). The *adhesions resulting from appendix disease* may be suggested by (1) an abnormal, fixed, position of the colon sigmoideum, (2) a pulling down of the stomach toward the right lower quadrant, with limitation of movement on respiration, or (3) signs of ileal adhesions or stasis.

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vi. The Form, Size and Position of the Colon transversum, the Colon descendens, and the Colon sigmoideum

The position of the **colon transversum** is almost never horizontal. Usually there is a marked kink at the flexura coli dextra; then a loop formation follows with convexity downward, the transverse colon finally ascending obliquely to the left, ending high up at the **flexura coli sinistra,** which is, as a rule, fixed in the left upper quadrant. In *enteroptosis,* a high grade of "transversoptosis" may be seen, the transverse colon often descending into the pelvis, in which event, it, together with the colon ascendens on the right, and the **colon descendens** on the left, which nearly always runs straight downward, yields an **M**-like picture. *Stasis at the flexura coli sinistra* may occur owing to abnormal kinking, to peritoneal adhesions, or to the formation of colonic veils or membranes. *Redundancy* of the **colon sigmoideum** is a very common finding, this part of the colon sometimes reaching over so as to overlap the appendix region. The sigmoid colon is subject to great variations in position. *Partial obstruction* at the junction of the colon

Fig. 350.—Marked Redundancy of Transverse Colon with Adhesions in Lower Right Quadrant. Probably Due to Appendicitis. (By courtesy of Dr. Baetjer and Dr. Waters, X-ray Dept. J. H. H.)

sigmoideum with the rectum is a relatively frequent finding, and one of the most important causes of chronic constipation. Adhesions or obstruction here prevent the normal uprising of the pelvic colon during defecation. Obstructions in the

Fig. 351.—Dislocation of, and Obstruction to, the Colon, Due to Tumor of the Liver. Redundant Sigmoid and Prolapsed and Redundant Transverse Colon with Evidence of Obstruction at the Hepatic Flexure. 1. Splenic Flexure; 2. Transerse Colon; 3. Obstruction at Hepatic Flexure; 4. Ascending Colon; 5. Descending Colon; 6. Rectum. At Operation a large Fungoid Carcinoma (Size of an Orange) of the Liver Pressing on the Hepatic Flexure was Found. There was no Infiltration of the Intestines. (By courtesy of Dr. Baetjer and Dr. Waters, X-ray Dept. J. H. H.)

course of the colon, especially at the lower end of the sigmoid, appear to have frequently, as their result, *insufficiency of the valvula coli.*

Dislocations of the colon caused by *abdominal tumors* have been studied especially by Stierlin (1912). Thus, *tumors of the kidney* are prone to dislocate the colon toward the median line. *Tumors of the spleen* usually lie in front of the

colon without displacing it. *Pancreatic and retroperitoneal tumors* may displace the colon transversum downward. *Psoas abscess and iliac abscess* dislocate the cecum and ascending colon medialward. Large *uterine tumors* compress the pelvic colon (upper rectum), while the cecum and colon ascendens and the colon transversum are shoved upward.

If the transverse colon and the ileum contain contrast material, while the cecum and ascending colon are empty, it is a sign of hyperesthesia of the empty part, a common finding even in the early stages of *ileocecal tuberculosis* (*Stierlin's sign*).

In *cancer of the colon,* there may or may not be marked obstruction. Should *marked obstruction* exist, its situation will be most quickly revealed by a contrast enema. If there be *no marked obstruction,* a filling-defect in the shadow of the contrast-filled colon may be observable. If the growth be of a cauliflower type, this may be digitated, while if it be of the annular type, the filling-defect will also be annular.

When abnormal conditions are found in the intestine on x-ray examination, one should never be satisfied with a single observation, but the examination should be repeated a day or two later, and unless the first findings are verified, not much stress should be laid upon them. Furthermore, a diagnosis should not be made until the *whole alimentary tract* has been thoroughly studied by the x-ray method, as well as by ordinary methods. There has been a little too much expected of the x-ray specialists by physicians. They can be of enormous help to us, but we must, in the first place, give them a fair chance, by permitting them the opportunity to make as thorough a study as they may deem necessary; furthermore, the other methods of clinical diagnosis should also be utilized to the fullest extent. In this connection, the words of a distinguished American röntgenologist should be heeded when he says: "Röntgenology may become a two-edged sword. The damage and danger of its use cannot be overestimated when röntgenograms are used by the surgeon to demonstrate a preconceived diagnosis and to force the patient to submit to surgical procedure. . . . The use of röntgenograms as a weapon with which to urge surgical procedure for some preconceived diagnosis should be vigorously condemned."

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3. Special Methods of Examination of the Rectum and Sigmoid Colon

In most cases, palpation of the rectum combined with inspection of the anus suffices; in some cases, however, an inspection of the interior of the rectum (proctoscopy), or of the rectum and sigmoid (proctosigmoscopy or rectoromanoscopy) may be desirable.

(*a*) *Palpation of the Rectum*

The patient lies on his left side, in the Sims's position (legs flexed and thighs drawn up on the abdomen, the upper thigh drawn up further than the lower). The physician introduces the index finger (covered with lubricated rubber glove or finger cot) of his right hand through the anus, supporting the thumb of the same hand on the perineum, while with his left hand he presses the pelvic contents firmly downward toward the pelvic floor in order that the palpating finger may reach as high up into the bowel as possible. At the moment of introduction the patient will suffer less comfort if he obey the injunction to "bear down" against the entering finger.

Attention should be paid to the presence or absence of **hemorrhoids** or piles (varicose dilatations of the rectal veins), which may be *external* (outside the sphincter ani and visible to the eye), or *internal* (within the sphincter and invisible, except on instrumental inspection).

The *state of the wall* of the rectum, in its different parts, is next determined (search for ulcers, fissures, fistulae, foreign bodies, strictures, nodular infiltrations from carcinoma, etc.).

In the male, the size, shape, consistence and tenderness of the *prostate* are felt for. Normally, the consistence of the *seminal vesicles* is such that they cannot be distinctly outlined, but when they are diseased, they may be felt as thickened cords attached like two horns to the prostate.

In the female, the back of the *uterus* can be distinctly palpated through the rectum, and also the *appendages* of the uterus; in virgins, such rectal examination should be preferred to vaginal examination except when the latter is absolutely necessary.

(*b*) *Inspection of the Rectum and Sigmoid*

The mucous membrane of the cavity of the rectum can be directly inspected by introducing a rectal speculum (*proctoscopy*), or, it may be examined along with the mucous membrane and cavity of the sigmoid, by the procedure known as *rectoromanoscopy*, or *proctosigmoscopy*.

The Rectal Speculum.—On introducing a rectal speculum, Kelly's proctoscope may be used, with the aid of a head-mirror or an electric

illuminator, the bowel having been previously thoroughly emptied. The patient, undressed, except for a light night-gown, assumes the knee-breast posture. The end of the speculum is well oiled and passed through the anal orifice in a direction slightly downward. If it be pushed in a little way and then quickly withdrawn, the anal orifice will at first contract vigorously and then relax. During this relaxation, the speculum should be passed in quickly before another contraction takes place. After it has entered for a distance of two inches, its further introduction should be controlled by the eye looking through its lumen into the bowel. On removing the obturator, air rushes in and distends the rectal canal. The ampulla recti can be fully inspected, together with its folds. As the instrument is gradually withdrawn, the mucous membrane is closely observed (inflammations, erosions, polyps, cancer, stricture, lues, tuberculosis). Kelly's instrument is much more serviceable and is safer than the various bi-valve and tri-valve specula formerly employed.

The Sigmoidoscope.—If sigmoscopy is to be practiced as well as proctoscopy, then a longer instrument must be used, either Kelly's sigmoidoscope, or the instrument devised by Strauss, in which, by a bellows attachment, the intestine can be gently distended with air in advance of the passage of the instrument when required. The patient should be especially prepared for examination. On the morning of the day before, a purgative is given, so as to secure purgation before evening. In the evening, two cleansing enemata are administered, one hour apart. In the morning, on the day of examination, it is desirable that the intestine be quiet; if necessary, a small dose of opium is given.

The Strauss sigmoidoscope consists of a metal tube, 30 cm. long and 2 cm. thick, provided with an obturator. The intestine and bladder having been previously emptied, the patient is placed in the knee-breast position on an operating table, and the instrument, well lubricated and gently warmed, is passed through the perineal part of the rectum, almost horizontally for a distance of 5 cm. The obturator is now removed and the electric light put in its place. Under the guidance of the eye, the tube is shoved in by lifting its inner end until the mark 11 cm. is reached, as the tube is now nearly at the beginning of the sigmoid, it is again directed horizontally until the entrance to the sigmoid becomes visible. If the entrance be not easily seen, the outer opening of the tube may be closed by a glass window and air blown in slowly until the opening appears. The instrument is then passed into the sigmoid, the end of the tube being somewhat depressed as it passes through the rectal limb of the sigmoid flexure. The tube may be passed in for a distance of from 30-50 cm. The greatest care must be exercised to avoid trauma, especially in the sigmoid, which may be friable. One must be most cautious if adhesions, neoplasms, or strictures offering marked resistance, be met with.

The examination goes on during the introduction of the tube, but the exact diagnostic inspection is to be made during its slow withdrawal.

One inspects, (1) the anus, (2) the pars analis recti or pars sphincterica (4.5 cm. long), with its columnae rectales and sinus rectales, and

especially the hemorrhoidal ring (annulus hemorrhoidalis), (3) the ampulla recti (6.7 cm. long), (4) the entrance to the sigmoid colon (11 cm. from the anal opening), and (5) the rectal limb of the sigmoid colon itself (for a distance of 18-20 or more cm.).

The normal appearances of the different parts met with are well illustrated in Strauss' monograph. In the *pars sphincterica*, one may find inflammations, erosions, fissures, polyps, hemorrhoids, perineal hemorrhoidal excrescences, fistulas, etc. In the *ampulla*, one may see inflammations (proctitis ampullaris), ulcers, polyps, stenoses or carcinomata. At the *entrance to the colon sigmoideum*, one may see inflammations, scars, pseudopolyps, genuine polyps, ulcers, carcinomata. In the *sigmoid colon itself*, one may see inflammatory processes (sigmoiditis), ulcers, hemorrhages, polyps, benign or malign neoplasms (excision for diagnosis), diverticula, or stenoses (from spasms, scars or neoplasms).

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4. Examination of the Functions of the Intestine (Motor, Secretory, and Absorptive)

(*a*) *Physiological Introduction*

The small and large intestines play an important part in digestion. The chyme, entering the duodenum from the stomach, is further acted upon by the pancreatic juice, the bile, and the succus entericus, with formation of substances capable of absorption by the intestinal wall. These substances, together with much of the water, are absorbed and in part synthesized to higher units by the intestine. The residue of the food, together with certain substances excreted by the intestine, are given off as the feces.

Succus entericus.—The intestinal juice proper (succus entericus) contains several ferments, including small amounts of amylase, much maltase, some invertase, and also lipase. Lactase is present in the young, splitting lactose or milk sugar into dextrose and galactose.

The most important ferment of the succus entericus is *erepsin,* a true peptase, which is capable of splitting polypeptids unaffected by tryptases into their constituent amino acids. In digestion, its main function is, therefore, to carry the splitting of the polypeptid mixture begun by trypsin to its termination. It acts best in feebly alkaline mixtures, but is very sensitive to strong alkali. This juice also contains *enterokinase,* which is an activator for trypsinogen, converting it into the active trypsin. The other constituents of the intestinal juice include salts, a little protein, and mucus. The reaction is feebly alkaline.

The ferments of this intestinal juice come chiefly from the glands of Lieberkühn. The secretion of Brunner's glands in the duodenum contains pepsin but no erepsin; otherwise its ferments are the same as those of the intestinal juice.

Pancreatic Juice.—The pancreatic juice is probably the most important factor in intestinal digestion, being produced in large quantities and containing three very important ferments, (1) *trypsin,* (2) an *amylase,* and (3) a *lipase.* All three ferments are formed in the gland as zymogens and are converted in the intestine, by kinase, into active ferments.

There is both a nervous and a chemical *regulation* of pancreatic secretion. The *nervous regulation* is by means of the N. vagus (secretory), and the N. splanchnicus (inhibitory), these two nerves in turn being subject to stimulation by substances circulating in the blood and arising in the glands of internal secretion.

A direct *chemical regulation* through the absorption of a hormone known as *secretin* into the blood and its action directly on the pancreatic cells is very important. The secretin has its origin in a prosecretin present in the mucous membrane of the duodenum, which, acted upon by the acid chyme from the stomach, gives rise to secretin.

If the food be rich in fats, much lipase is produced; if it be rich in starch, much amylase; if rich in protein, much trypsin. The pancreas responds almost slavishly, in ferment-production, to the amounts of particular food stuffs entering the intestine.

Bile.—The bile plays a subsidiary, though a still important, part in intestinal digestion. Its functions are not yet fully clear. It contains no ferments except a slight amount of amylase. Its most important function appears to be related to the *digestion of fats.* As soon as small amounts of fatty acids are formed, these unite with the biliary acids to form soaps, which, in turn, make very fine emulsions with other fats, thus placing the latter in the most favorable state for cleavage.

The salts of the biliary acids give rise to active lipase by acting upon its zymogen. The bile has a similar but feebler action on trypsinogen. The bile also helps to destroy pepsin, a desirable function, since pepsin, if left active, would injure trypsin and erepsin.

Another important function of the bile is its *stimulation of intestinal peristalsis.* Some of the constituents of the bile probably exert no effect upon digestion, but are to be regarded as pure excretory substances to be thrown off with the feces.

A diet rich in meat stimulates biliary secretion, the stimuli acting apparently in the duodenum (through albumoses).

Bile is continuously secreted, but is intermittently poured out into the intestine, collecting in the gall-bladder, which acts as a reservoir, in the intervals. To increase the number of times the bile is emptied into the intestine, one increases the number of meals taken per day. Advantage is taken of this fact when it is desired to close

a biliary fistula; small meals are then given every two hours through the day and night.

Digestion in the Intestine.—The chyme enters the intestine, not continuously, but in single portions; after the passage of each acid portion through the pylorus the latter is closed by a reflex, and opens again only when the duodenum becomes alkaline. This chyme is permeated with HCl and pepsin and contains, besides, fat, starch, and cellulose, some undigested albumen and the albumoses and peptones resulting from gastric digestion. In the cap, or pars superior duodeni, gastric digestion is continued for a time, until the chyme is sucked out by the broad peristaltic contractions of the pars descendens duodeni. The contents of the cap are still feebly acid. In order that the ferments of the mixed juices in the intestine may act upon this mixture, the HCl of the mixture must be neutralized and the pepsin destroyed. The alkaline succus entericus can neutralize the mixture, but only after it has passed some distance through the intestine. It is the alkaline bile and pancreatic juice that are chiefly responsible for neutralizing the HCl. In addition, the biliary acids form insoluble precipitates with the protein residues and these precipitates carry down with them the pepsin. These precipitated masses are gradually dissolved by the intestinal juice.

The **digestion of carbohydrates,** begun by the amylase of the saliva, is now completed, with formation of sugar, through the activity especially of the amylase and maltase of the pancreatic juice, any cane sugar being split by the invertase of the intestinal juice.

The **digestion of fats** results from the action of lipase, made effective by the biliary salts of the biliary acids, with formation of fatty acids and glycerin. Whether the lecithin of the food is also split before absorption is not known.

The **digestion of proteins** also proceeds, the products of peptic digestion being further acted upon by the trypsin (activated by enterokinase). Tryptic digestion gives rise to simple polypeptids, and even splits some of the polypeptids, especially those containing tyrosin and tryptophan, into their constituent amino acids. Certain of the polypeptids, however, resist the action of trypsin, but they are split by the erepsin of the intestinal juice so that, ultimately, in normal digestion, all the protein of the food is broken up into its constituent amino acids. There is some evidence that polypeptids, and even higher complexes, can be absorbed as such. After feeding large quantities of egg albumen, some of it can be demonstrated in the blood serum by means of precipitin reactions.

Certain **indigestible substances,** especially cellulose, pass through the intestine without being absorbed. These, together with desquamated epithelial cells, mucus, the excretory portions of the secretions, and large numbers of bacteria, pass from the small intestine into the large intestine, along with residues of protein, fat, and starch that have not been digested and absorbed in the small intestine. Two forms of **fermentation** then appear, (1) putrefaction of protein, and (2) fermentation of carbohydrates, especially of cellulose.

From the *protein putrefaction,* amino acids are first formed, and, later, from them, fatty acids, phenol and indol are derived. Parts of these substances are absorbed, the fatty acids being used as food substances, the aromatic bodies (which are poisons) being detoxicated by union with sulphuric acid or glycuronic acid to form esters, after which they are excreted through the urine. The unabsorbed portion of these substances passes out in the feces.

The *fermentation of carbohydrates* (cellulose) by bacteria gives rise, first, to glucose, some of which may be absorbed. Other products, like lactic acid and butyric acid, are also formed and can be utilized in metabolism. Gases, like hydrogen and methane, cannot be used and pass off as flatus.

In general, it is believed that the putrefaction of proteins is harmful to the organism, and the fermentation of carbohydrates helpful. An abundant carbohydrate fermentation seems to be antagonistic to the putrefaction of proteins; hence the advantage of a diet rich in cellulose and of the administration of bacillus bulgaricus in persons suffering from excessive protein putrefaction.

Absorption from the Intestines.—The absorption of dissolved substances produced during digestion occurs almost wholly from the small intestine, where the absorptive surface is enormously increased by means of the villi intestinales and the plicae circulares [Kerkringi]. Here, filtration processes, diffusion processes, and osmotic processes, play a part, as well as specific selective absorptive work, done by the epithelial cells.

Water and most neutral salts are absorbed very quickly. Iron is the only one of the salts of the heavy metals to be absorbed. Sodium chlorid is easily absorbed, sodium sulphate and magnesium sulphate only with difficulty.

Of the carbohydrates, only monosaccharides can be absorbed. Disaccharides must be first split; thus, milk sugar will not be absorbed if lactase be absent, or, at any rate, not until fermented by bacteria.

Proteins appear to be capable of absorption, to some extent at least, in all stages of disintegration. Most protein, however, undergoes complete disintegration into amino acids before absorption. A small amount may be absorbed in the form of polypeptids, minute amounts as peptones, albumoses, or even as albumens.

Fats appear to be absorbed (after being split into fatty acids and glycerin) in the form of soaps, to be resynthesized to neutral fats in the intestinal wall. Whether some fat is directly absorbed, in the form of emulsion, or not, is undecided.

Some of the substances absorbed pass through the lymph spaces into the thoracic duct, and so into the blood. Most of the substances absorbed enter the blood vessels, and pass by way of the portal vein to the liver, where many toxic substances are neutralized or destroyed.

The passage of the contents through the intestinal canal depends on its motility (*q. v.*). The rate of progress is very rapid in the small intestine; the sojourn in the large intestine is much longer. In the large intestine, the water is slowly absorbed with ultimate formation of firm (solid or semisolid) feces.

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(*b*) *Examination of the Motility of the Intestine*

i. Determination of the Ingestion-defecation-time by Carmine Marking

To determine the length of time required for the food residues of a given meal to pass through the stomach and intestine and be eliminated as feces, one gives a capsule, or conseal, of 0.3 grams of carmine with the first portion of the food eaten. The corresponding feces will, on appearance, be stained red. While such a test informs us as to the total time required to pass through the whole digestive tract, it gives no clue to the motility of the single parts of the digestive tube. To determine the latter, we resort to röntgenological study after a "contrast-meal." The method of carmine-marking is, however, very useful in connection with metabolic work, since it permits us to collect the feces that belong to the period of a given experiment. Instead of carmine, charcoal may be used.

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ii. Motility of the Intestine Studied Röntgenologically

The physiology of intestinal motility has been carefully studied röntgenologically in small animals by W. B. Cannon, Elliott and Barclay-Smith, and Gruetzner, whose papers should be familiar to clinical workers. Since clinical röntgenologists have undertaken the study of the motility of the human intestinal tract, it is surprising to find how closely observations of the human phenomena agree with those made upon cats and dogs in the laboratory. Röntgenoscopy after a contrast meal is the most important method, though serial röntgenography and röntgencinematography are also useful, especially for making permanent records. In this country, papers have been published especially by J. T. Case, L. G. Cole, Hemmeter, Ashbury, Pfahler, F. H. Baetjer and J. Friedenwald, and George and Guerber; while in Europe, publications have been made by Holzknecht, Fischl and Porges, Elliott and Barclay-Smith, Rieder, Stierlin, Kästle, Schwarz, Groedel and others.

The methods of administering the contrast meal and the contrast clysma have already been described, as well as the times at which, normally, the contrast material arrives in the different portions of the gastro-intestinal canal (See Röntgenology of Size and Position of the Intestine, and Röntgenology of Gastric Motility). Here, attention will be called only to the phenomena of motility, demonstrable by x-ray methods, in different parts of the intestine.

(1) *Motility of the Duodenum*

The motility of the **pars superior duodeni** (the "bishop's cap," the "pilleus ventriculi," or "duodenal bulb") has been referred to in connection with gastric

motility with which it is so intimately connected. The *hypermotility* and *rapid emptying of the cap,* as well as of the stomach, in duodenal ulcer have been emphasized. They may occur with any irritation in the right upper quadrant (gall-stones, adhesions). They are also seen when there is anacidity of the gastric juice (achylia gastrica; some cases of carcinoma ventriculi).

Spasm of the cap, causing constriction and an appearance as though it had been twisted or wrung empty of its contents, the bismuth in the distorted lumen casting a corrugated or fluted shadow, is often the result of lesions far distant from the cap (appendicitis, ileal stasis, etc.). Writhing of the cap can sometimes be elicited on röntgenoscopic examination, simply by making pressure at the duodenojejunal flexure.

Retention in the cap, along with a delayed emptying of the stomach, is often due to *inhibition of duodenal peristalsis,* which, in turn, appears very often to be due to a distention or a dilatation of the terminal portion of the ileum. How this inhibition is brought about we do not know, though Cole's suggestion seems plausible that it may be due "to reflex curtailment of the amount of the biliary and the pancreatic secretion so that there is a cessation of the alternating alkaline and acid reactions of the pars descendens duodeni, the exciting cause of the propulsive duodenal peristalsis, which normally evacuates the cap and propels the food through the duodenum and jejunum." It is probable too that prolonged retention in the cap is a source of danger, favoring the occurrence of duodenal ulcer. When duodenal peristalsis is inhibited, the stomach may force chyme past the cap into the pars descendens and the pars inferior but not into the jejunum.

The motility of the **pars descendens duodeni** and of the **pars inferior duodeni** is normally characteristic. In this part of the intestine the plicae circulares (Kerkringi) are very high and when the contrast-material is passing through they give rise to oblique or horizontal bands of pallor alternating with oblique or horizontal shadows. The motility is characterized by (1) a broad, rapid, periodical propulsive peristalsis, and (2) a churning or mixing motion of the circular folds. The pars descendens by means of its peristalsis sucks the chyme out of the pars superior (or cap) and propels it in fingerlike masses (Holzknecht) into the pars inferior and the jejunum. When the chyme does not enter the jejunum, either owing to failure of duodenal peristalsis, or to obstruction at the duodenojejunal flexure (as in angiomesenteric ileus), the so-called *sausage-shaped duodenum* of Holzknecht appears; in this condition, duodenal contents may be forced into the ampulla of Vater and be the starting point of an infectious cholangitis or a pancreatitis.

(2) *Motility of the Jejunum and of the Ileum*

The **intestinum jejunum,** or **empty intestine** was well named; the passage of the contents through it is so rapid that one rarely sees it dilated or even filled. The *flocculent appearance* of the contents seen röntgenoscopically or on serial röntgenography has already been referred to.

The **intestinum ileum,** or **twisted intestine** is also well named. F. P. Mall has demonstrated the constancy of the position of the coils in most cases. The röntgenological criteria (location, coagulalike masses, wormlike coils) have already been described (See Examination of Size and Position of the Intestines). The contrast-material remains longer in the ileum than in any other portion of the small intestine, much longer than the short period of residence in the duodenum and the jejunum.

The disturbance of motility associated with **ileal dilatation** has been much discussed. Why, aside from neoplasm, does ileal stasis occur? Why does not the

ileum, in such cases, empty itself within normal time into the cecum? We now know that kinking of the terminal ileum (*Lane's kink*) though it does occur, is rare, and not a common cause of ileal stasis and dilatation. *Peritoneal adhesions* obstructing the terminal ileum are also relatively unimportant. The two most common causes are (1) *spasm of the ileal-sphincter mechanism,* or the muscle of the wall of the terminal 4 inches of the ileum (a region that A. Keith has shown to possess a special tonic function; it acts as a sphincter (a) to prevent the ileal contents from passing too quickly into the cecum, and (b) to help form a barrier against the regurgitation of the contents of the cecum into the ileum); and (2) *incompetency of the valvula coli* (or ileocecal valve), due most often to some form of colonic stasis, and demonstrable in one out of about every six cases presenting gastro-intestinal symptoms.

Hertz suggested ileocecal-sphincter spasm as a cause of ileal stasis in 1908, and in 1913 Case, independently, advanced a similar idea; a common cause of this spasm is appendiceal irritation. Case believes, however, that incompetency of the valvula coli is responsible for the majority of cases of ileal stasis; the special method of demonstrating it has been described on page 382. Kellogg, of Battle Creek, has devised a simple operation for repairing an incompetent valvula coli, and another for constructing a similar competent valve in cases in which it is necessary to perform ileosigmoidostomy. It is, however, rarely necessary to resort to surgical treatment in cases of ileal stasis; much of the surgical activity in this connection has undoubtedly been misdirected.

(3) *Motility of the Large Intestine*

In the **intestinum crassum,** or **large intestine,** the motor phenomena are complex. At least four types are distinguishable: (1) peristalsis, (2) antiperistalsis, (3) tonic constrictions and (4) haustral churning. The large intestine is functionally divisible into two parts, at a point in the right half of the colon transversum where a tonic constriction ring, known as Cannon's ring, is often visible. The first part, often referred to as the **proximal colon** or **near-colon,** includes the intestinum cecum, the colon ascendens, and the portion of the colon transversum to the right of Cannon's ring; the second part, often referred to as the **distal colon,** or **far-colon,** includes the portion of the colon transversum to the left of Cannon's ring, the colon descendens, the colon sigmoideum and the intestinum rectum. (Strictly speaking, the cecum and the rectum are not parts of the colon; they, together with the different parts of the colon, make up the whole intestinum crassum.)

Motility in the Proximal Colon.—The prevailing movement in the large intestine from the cecum to Cannon's ring is **antiperistalsis**—the **anastalsis** of Cannon. Waves of contraction pass proximalward from the region of Cannon's ring to the cecum. The waves appear in series, about 5 waves per minute occurring for 4 or 5 minutes at a time. This anastalsis is excited by the pushing of fresh material from the ileum into the cecum and ascending colon; at such times, the *tonic constriction ring* of Cannon is stretched (from the colonic distention) and begins to pulsate; with each pulsation of the ring, a wave of antiperistalsis (or anastalsis) is started at the ring and travels toward the cecum. The *function* of this anastalsis appears to be the retention of the contents in the proximal colon long enough for much of the water to be absorbed; the soft, mushy contents are thus converted into the firmer contents of the distal colon. These anastaltic waves of the proximal colon, so easily studied in animals, have also been repeatedly observed in man on x-ray examination (Rieder, Case). In one instance, Case observed no less than five

anti-peristaltic waves in progress at the same time between the middle of the right half of the colon transversum and the cecum.

A *rhythmical to-and-fro shifting* of the contents of the proximal colon has

Fig. 352.—First Stage of a Mass Peristaltic Movement of Holzknecht in the Colon. (Courtesy of Dr. Jas. T. Case.)

occasionally been observed when no anastaltic waves were visible (Bloch, v. Bergmann and Lentz); it can often be stimulated by palpation. Whether this "retrograde transport" is due simply to relaxation of the proximal bowel after a peristaltic

contraction has forced material onward, or is the result of a presumable anastalsis despite the absence of visible waves, is still uncertain.

In the proximal colon, too, onward waves of peristalsis—Cannon's diastalsis—

Fig. 353.—Second Stage of a Mass Peristaltic Movement of Holzknecht. About Four Seconds Elapsed Between This Exposure and That of the Preceding Picture. (Courtesy of Dr. Jas. T. Case.)

also occur, from time to time. As this form of motility is most characteristic of the distal colon, its features will be described there. Haustral churning too is not

a marked feature of the proximal colon; it does occur in this region, but the haustra coli are but poorly developed in the near-colon.

Motility in the Distal Colon.—The predominant type of movement in the distal colon is onward peristalsis; here, haustral churning is also a prominent feature; and, to a certain extent, antiperistalsis also occurs.

Onward peristalsis, or the **diastalsis** of Cannon, occurs in man in the distal colon (from Cannon's ring analwards) in at least two forms: (1) the mass movements of Holzknecht, and (2) the slow propulsive movements of small thumb-size fragments as described by Fischl and Porges.

The **mass movements** of Holzknecht are exceedingly interesting. Holzknecht asserted that they occur three times in twenty-four hours, at about eight-hour intervals, each movement lasting only a few seconds. At the first movement, the masses collected in the cecum and ascending colon are shoved, in a few seconds, through about one-third of the whole length of the colon. Later on, there is a second abrupt movement forward to the colon descendens, lasting only a few seconds. The third of these movements is the last in the large intestine. Some of these mass movements were luckily observed by röntgenoscopy. Röntgenograms made in the intervals registered the contents wherever these happened to be at rest. Only by frequent röntgenoscopic examinations can the actual movements through the large intestine be "caught."

Recently (1914), J. T. Case has given us an admirable description of this mass peristalsis as he has observed it in no less than thirty-seven different persons; the movement was seen in the majority of instances in the colon transversum and the colon descendens. "The bowel contents suddenly lose their haustral markings and are formed into an ovoid, sausage-shaped mass, with perfectly smooth edges and rounded at the ends. This mass travels at about twice the rate of peristaltic waves in the stomach. . . . After the mass comes to rest, the haustral indentations reappear, the time required for the reappearance depending upon the consistency of the bowel content—quickly if the content be semifluid, more slowly if the bowel content is of a firmer consistency."

The slow propulsive peristalsis causing **onward movements of small thumb-size fragments,** as described by Fischl and Porges, has also been seen by many observers. Case describes having seen "small boluses, the size of pigeon's eggs, travelling slowly down the descending colon into the pelvic colon."

In the distal colon **haustral segmentation,** or **haustral churning,** is a well known phenomenon, familiar to every one who studies the large intestine röntgenologically. It goes on constantly, serves to keep the colonic contents plastic, and assists in their progress analwards. Sometimes, *large pendulumlike movements,* first described by Rieder, are also seen; according to Case, they are always precursors of mass movements. While onward peristalsis or diastalsis and haustral churning are the prevailing activities of the distal colon, antiperistalsis also undoubtedly may occur. Rieder described it, and Case mentions an instance in which he saw a "bolus of ingested bismuth the size of a banana carried from the pelvic colon backward into the left half of the transverse," and on four other occasions he has seen "smaller boluses of bowel contents, varying in size from a filbert to a walnut," carried from the colon sigmoideum oralward as far as the flexura coli sinistra.

Exaggerated antiperistalsis in the large intestine is a sign of serious bowel obstruction (J. T. Case). It may always be seen in cancer of the colon causing obstruction; it is not uncommon in the temporary obstruction of spastic constipation, and doubtless accounts for the filling of the large intestine frequently observable after ileosigmoidostomy.

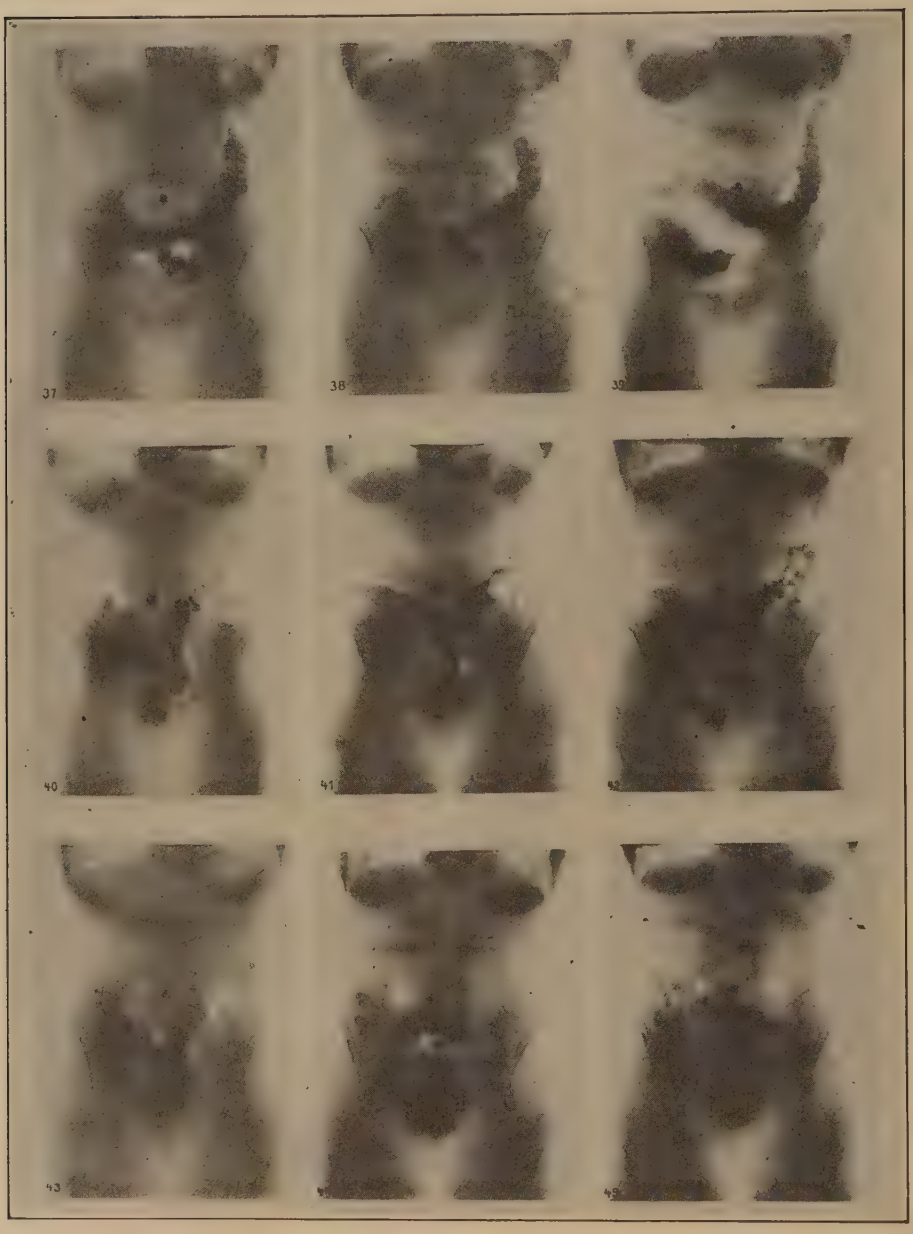

Fig. 354.—Rieder's Large Pendulum Movements. Notice the Snakelike Dislocatory Movements of the Colon. These Nine Röntgenograms of the Abdomen Were Made at Half-hourly Intervals, the Position of the Patient and of Other Circumstances Being the Same, Except For the Lapse of Time. The Pictures Prove the Futility of Attempts to Attach Very Much Importance to the Position of the Transverse Colon, Which Normally Should Be Freely Mobile. (Courtesy of Dr. Jas. T. Case.)

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iii. Intestinal Obstruction

In intestinal obstruction there is dilatation of the intestine on the proximal side, with hypertrophy of its walls, confirmable by x-ray studies.

When the obstruction is complete (*ileus*), or nearly complete, intestinal putrefaction occurs in the proximal portion with powerful antiperistalsis; if the obstruction be in the large intestine, this soon causes

incompetency of the valvula coli, and leads finally to fecal vomiting. Feces and fluids are no longer passed *per anum.* The contours of single intestinal loops may give rise to characteristic abdominal "patterns." The importance of simple inspection of the abdomen for the recognition of visible peristalsis due to intestinal obstruction has already been referred to. There is oliguria and indicanuria. In such cases, one seeks for the *cause of the ileus* (tumor, foreign body, feces, adhesions, strictures, intussusceptions, invaginations, hernias, compression from without, etc.), and its *site.* All hernial orifices should be carefully examined and a thorough rectal examination made. The lower the site of the obstruction, the greater the meteorism and the tendency to fecal vomiting; the higher the site of the obstruction, the less the meteorism and the greater the intoxication. If the obstruction be in the duodenum or jejunum the vomitus is not fecal but contains bile. Obstructions involving this region are violently toxic. Recently, the toxic substance produced in closed duodenal loops has been studied experimentally (Whipple, Stone and Bernheim).

In acute obstructions, exploratory laparotomy may be so urgent that x-ray studies dare not be awaited; in chronic obstructions, the bismuth x-ray helps enormously in diagnosis. (See Special Diagnosis of Diseases of the Intestine.)

iv. Defecation

The mechanism of defecation is a complicated reflex, involving the smooth muscle of the colon and rectum, on the one hand, and the striped muscle of the M. sphincter ani externus, of the M. levator ani, and of the muscles of the abdominal wall, on the other. After the feces have reached a proper consistence, they accumulate in the sigmoid colon. The rectum normally fills just before defecation.

The process of defecation in man has been studied by the x-ray method, confirming Cannon's studies in the cat. A long column of feces is passed out at one time—a mass movement of Holzknecht, the entire large intestine below the splenic flexure being normally evacuated at a single act. The feces accumulating in the distal colon do not pass the junction between the pelvic colon and the rectum until there has been special stimulation of colon-peristalsis by the eating of breakfast, or by the muscular activities attending rising and dressing; this causes some feces to enter the rectum, when the sensory nerves are stimulated and the desire to defecate is aroused. In the absence of a normal "call," voluntary contraction of the abdominal muscles may cause feces to enter the rectum and start the reflex. During the act of defecation, contraction of the diaphragm and of the abdominal wall leads to an increase of the intra-abdominal pressure, 4-8 times the normal. The feces, entering and distending the rectum, arouse reflexes that start strong diastaltic contractions of the colon and relaxation of the anal sphincters.

The act of defecation is under the dominion of the autonomic nervous system.

Here, as everywhere in autonomic domains, there are antagonistic innervations; on the one side the N. erigens, on the other the N. sympathicus. In the spinal cord, the segments in the conus medullaris exercise control, and they in turn are subject to cerebral influences (See Examination of the Nervous System).

Involuntary Defecation (Incontinentia alvi).—This may occur in tabes, in general paresis, in cerebral atherosclerosis, and in other brain diseases; it occurs also in acute diseases in which consciousness is disturbed (*e. g.,* in typhoid fever). For a fuller description see Part XII.

Frequency of Defecation.—When we recall that the distance from the pylorus to the rectum averages about eight meters and think of the remarkable team-work that must exist among the different forces in order to bring about the same final act of defecation at definite intervals of time, and of what a variety of hindrances may interfere with the processes, we cannot help but be astonished at the regularity that, normally, prevails.

Nothing is more striking than the temporal precision of the work of the intestine when the digestive apparatus is normal, the need of defecation being felt once in twenty-four hours at approximately the same time. Here, much depends upon the cultivation of a *habit*, and young children should be taught to go to stool regularly just after breakfast each morning, whether inclined to do so or not, until the habit of defecating at that hour is regularly established. A desire to defecate at any other time of day should be inhibited when possible.

There are, however, numerous exceptions to this normal regulation. Some people defecate thrice daily and have normally-formed stools. Reichmann has reported cases where a spontaneous stool occurs only once a month, and in spite of the monstrous retention, no marked inconvenience was experienced. Some persons defecate at intervals of from 48-72 hours and feel well. Many, on the other hand, suffer marked discomfort whenever the interval between defecations is prolonged beyond twenty-four hours. A good many careless persons never have spontaneous movements, but resort always to artificial evacuation by purgatives or enemata.

Sucklings, normally, have two or three stools per day. The amount of food taken, and its character, influences the number of stools at all ages.

v. Constipation

This may be a sign either of organic, or of functional, disease. Thus it is sometimes a symptom of a serious organic disease, being common in gastric and intestinal catarrh, in intestinal stenosis, in peritonitis, in meningitis, and in tabes. It depends, sometimes, upon a local cause in the large intestine (atony, ptosis, adhesions, elongated sigmoid, Lane's kink, membranes and veils, incompetency of the valvula coli, spasm, etc.). In this country, some stress has been laid upon hypertrophy of the plicae

transversales recti ("Houston's valves"), and upon hypertrophy of the muscular wall at the junction of the colon sigmoideum with the intestinum rectum—the so-called O'Bierne's sphincter—as causes of chronic constipation. The most marked constipation accompanies ileus.

The relations of adhesions and intestinal angulations resulting from enteroptosis, to chronic constipation have been studied by R. C. Kemp.

Chronic constipation is most often due either to intestinal atony (*atonic constipation*), or to intestinal spasm (*spastic constipation*), though it may depend upon organic stenosis (carcinoma, stricture, pressure from without due to adhesions, to tumors or to displaced organs). When constipation sets in acutely, the bowels having been regular before, it may depend upon alteration of the mode of life, errors of diet, mental excitement, preceding diarrhea, the use of constipating drugs (opium, morphin), or some sudden organic occlusion (intestinal obstruction). In lead colic, too, the onset of constipation may be sudden.

When a mechanical hindrance to the bowel movements can be excluded, constipation is said to be functional. In the *functional cases*, the fecal masses may reach the sigmoid and even fill up the ampulla of the rectum, without exciting expulsion, owing to abnormalities of the defecation reflex (**proctogenous constipation**).

Some cases of constipation appear to be due to *over-utilization of the intestinal contents* with too good absorptive power, the result being (1) lessened residue and (2) lessened fluid in the intestine, with insufficient chemical stimulus to the motility of the intestinal wall.

In the so-called **spastic constipation,** stools of small caliber, ribbon-like or pencil-shaped, covered with mucus, are passed. It is common in genital irritation, in sigmoiditis, in colitis mucosa, and in irritations elsewhere in the abdomen (renal colic, gall-stones, pelvic inflammatory disease, chronic appendicitis, prostatitis). The constipation due to reflex inhibition of the intestinal movements from ulcer of the stomach, ulcer of the duodenum, or gall-stones, is sometimes spoken of as **gastrojejunal constipation.**

Recently, *röntgenological studies* have given up a clearer idea and a better classification of the constipations than we had before. Of 29 cases studied by Strauss and Brandenstein, 11 were of the "colon ascendens type," 6 were of the "sigmoidal type" or "proctosigmoidal type" and 12 showed "total stagnation" or "colostasis." Of the total stagnation cases, part were of the "uninterrupted type" corresponding to asthenic or atonic constipation, and part were of the "interrupted type" corresponding to erethic or spastic constipation. In the ascendens type, chronic typhlitis is common (*typhlitis stercoralis*). According to these authors, the separation into type gives clews for therapy, "sigmostasis" responding best to physical therapy, and "typhlostasis" yielding more often to pharmacotherapy and reduction of cellulose in the diet.

Several excellent books upon constipation and allied disorders are now available (See References).

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vi. Diarrhea

This may be acute or chronic. *Acute diarrhea* is usually due to gastro-intestinal catarrh, from errors of diet, intoxications, or one of the infectious diseases (typhoid, dysentery, cholera, sepsis). In cholera, *rice-water stools* are seen; in typhoid, *pea-soup stools;* in dysentery, blood, mucus, and sometimes pus may be present in the diarrheal stools.

Chronic diarrhea, or recurring paroxysmal diarrheas, may be due to organic diseases of the bowel (enteritis, tuberculosis, amyloid, etc.), or of other organs (cardiac insufficiency, cirrhosis of the liver, uremia, gastric anacidity). A *diarrhea in the early morning,* before breakfast, is often the first symptom complained of when free HCl is absent from the stomach. In *unexplained, "motiveless," diarrheas,* we should keep in mind the possibility of (1) achylia gastrica, (2) Graves's disease, and (3) tabes dorsalis (intestinal crises). The so-called *stercoral diarrhea,* accompanied by colic, and following two or three days of constipation, is a common phenomenon of habitual constipation, as is also the so-called *fragmentary defecation,* in which, every few hours, a small stool is passed with tenesmus and a feeling of incomplete defecation.

On *painful defecation* a careful examination of the anus and rectum should be made (see above).

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(c) Examination of the Secretory, and the Absorptive Functions of the Intestine

i. Introduction

Our methods for determining secretory disturbances of the intestine are as yet unsatisfactory, though some clews can be obtained (1) by observation of the symptoms, (2) by the examination of duodenal contents and (3) by examination of the feces.

The succus entericus itself, may be poor in ferments (erepsin, nuclease, maltase, and lactase). In extracts of normal feces, erepsin and maltase can be demonstrated (*q. v.*).

In acute and chronic diarrheas, there is an *increased transudation of serum* into the intestine, recognizable by the appearance of soluble protein in the feces.

Mucus is secreted in abnormally large amounts in intestinal catarrh, especially in catarrh of the colon; thus, in mucous colitis, actual casts, or large shreds of mucus, may be passed, with colicky pains. When the mucus comes from the small intestine, it is intimately mixed with the stool and presents a sago-grain appearance, being often stained with bile.

Imperfect digestion and absorption in the intestine may be due to *hypermotility,* to *disease of the wall* of the intestine, or to *insufficient pancreatic juice or bile.*

If there be great interference with digestion and absorption, the stools will be voluminous and will contain undigested muscle fiber and fat (so-called *pancreatic stools*). Such stools appear rarely, if ever, to result simply from interference with the flow of pancreatic juice, but are nearly always due to disease of the gland substance.

Gastric anacidity need not interfere at all with the absorptive power of the digestive tract, except through hypermotility. In icterus, in amyloid, and in intestinal tuberculosis, however, fat absorption may be considerably interfered with.

When much undigested meat passes in the feces, the condition is spoken of as

azotorrhea; when much undigested fat passes, the condition is known as **steatorrhea.**

Carbohydrates are usually absorbed well from the intestine, even in pancreatic disease and in icterus. Should the absorption of carbohydrates be interfered with (See Schmidt's Fermentation Test), it is usually due to faulty absorption in the small intestine resulting from catarrh of its mucous membranes.

We shall now pass on to (1) the examination of duodenal contents, and (2) the examination of the feces.

ii. Examination of Duodenal Contents

Duodenal contents can be obtained for examination, either (1) from the stomach, after the oil-breakfast of Volhard-Boldireff, or (2) directly from the duodenum, by means of Einhorn's duodenal pump, or with the aid of Gross's duodenal tube.

Method of Obtaining Duodenal Contents After an Oil-Breakfast (Volhard-Boldireff).—If food rich in fat be ingested, the duodenal contents regurgitate into the stomach; after an oil-breakfast, it is, therefore, possible to recover pancreatic juice, with or without bile, and practically free from gastric chyme, by means of the stomach tube. In the early morning, fasting, 200 c.c. of olive oil (*oil-breakfast of Volhard*), are introduced through a tube, and one half hour later the stomach contents are drawn off. Usually 50-100 c.c. of oil are recovered, together with a considerable amount of a watery, mucoid, often greenish, fluid; the latter is easily separable from the oil by means of a pipet or a separating funnel.

In the *breakfast of Boldireff*, fat and a fatty acid are combined. He gives 100-200 c.c. of a 2 per cent solution of oleic acid in olive oil, and draws off the stomach contents in from one half to one hour later; 20-30 c.c. of straw-colored, strongly alkaline, sticky, tough duodenal fluid can thus be obtained.

It is best thoroughly to neutralize the contents of the stomach before giving the oil-breakfast; accordingly, a small coffeespoonful of burnt magnesia, suspended in water (say 0.7 gram in 30 c.c. water), is swallowed just before the oil is given. Twenty minutes later, a second portion of burnt magnesia is swallowed. The stomach contents are then collected at the end of forty-five or sixty minutes.

Method of Obtaining Duodenal Contents Directly by the Use of Einhorn's Duodenal Pump.—An ingenious instrument known as the duodenal pump has been devised by M. Einhorn for collecting duodenal contents, and for duodenal feeding. It consists of a small perforated metal capsule (14 mm. long and 23 mm. in circumference), attached as a tip to a tube one meter long, marked in three places, I (= 40 cm.), II (= 56 cm.), and III (= 70 cm.) from the capsule, these marks corre-

sponding respectively to I the cardia, II the pylorus, and III the duodenum 10 cm. below the pylorus. To one end of the tube an aspirating syringe can be attached. On the day of examination, the patient takes only a liquid diet, and about a half hour before beginning the test, he drinks a cup of tea with sugar, but without milk. The capsule is moistened, placed in the pharynx, and swallowed with a drink of water. A little stomach-juice is drawn off for analysis. A small amount of water is then injected through the tube, which is then clamped and allowed to remain in position for about an hour, during which time the patient should not close the mouth tightly; he may occupy himself with

Fig. 355.—Duodenal Pump. (After Einhorn.)

reading or the like. Through the peristalsis of the stomach, the capsule is carried through the pylorus into the duodenum, and may even pass for some distance into the small intestine. At the end of one hour, the position of the tube is noted. If the mark III (70 cm.) have reached the lips, or a still greater portion have been swallowed, the examiner cautiously and slowly aspirates. If the capsule has reached the duodenum, a clear, golden yellow, or watery fluid, of alkaline reaction and viscid consistence, will be obtained; but if the tube be still in the stomach, an acid fluid will appear (the tube being rolled up in the stomach). In the latter

case, a little water is again injected through the tube and the tube withdrawn to the mark II (56 cm.), clamped again, and the patient left for another 30-60 minutes. It is usually possible, in this way, to pass a capsule into the duodenum, though in pyloric stenosis, or in pylorospasm accompanying hyperacidity, one may not be successful.

Another way of telling whether the capsule is in the duodenum, or is still in the stomach, consists in blowing a little air into the tube. If the capsule be in the stomach, the patient will feel the entrance of the air distinctly and can definitely localize the spot, but if the capsule be in the duodenum or jejunum, the entrance of air is not felt. Or, again, the patient may take two or three swallows of milk; on aspirating now, if the capsule be in the duodenum, a golden yellow or watery fluid unmixed with milk will be obtained; if it be in the stomach, milk, unaltered, or coagulated, will appear.

In addition to its use for collecting duodenal contents, Einhorn's pump has been found valuable for duodenal feeding in cases of gastric and of postpyloric ulcer.

Method of Obtaining Duodenal Contents Through the Duodenal Tube of Gross.—This tube consists of a perforated metal ball, twice as large as a pea, attached to a small rubber tube, 125 cm. long, with 10 cm. markings. With the latter, a glass bulb is connected, and it in turn is attached by a rubber tube to a mouth piece (for either oral suction, or aspiration by a bulb).

The patient takes, in the morning, a glass of milk and water (equal parts), and 30 minutes later the tube is introduced to the mark 45 cm. Air is then blown through the tube to straighten it out, after which the patient lies on his right side and the tube is allowed to slip in as far as the mark 60 cm. In five or ten minutes a first aspiration is made. Gradually (without swallowing-movements) the tube passes in as far as the mark 65 or 70. Then a second aspiration is made, and further aspirations at short intervals until fluid from the duodenum, neutral or feebly alkaline in reaction, is obtained.

Examination of Duodenal Contents Thus Obtained

The duodenal contents may now be examined for bile pigment and for pancreatic and intestinal ferments. Unless no pancreatic tissue is functionating, the pancreatic ferments will be found. To discover enfeeblement of pancreatic function, it is best to study the feces after the Schmidt-Strasburger test diet (*q. v.*).

Test for Bile Pigment in Duodenal Contents.—For this purpose, the ordinary Gmelin reaction may be used (See Examination of Urine).

Tests for Proteolytic Ferments (Proteases) in Duodenal Contents.—The mixture may contain pepsin, trypsin or erepsin. Since pepsin acts

only in an acid medium, the presence of trypsin can be determined by demonstrating the capacity of protein digestion (fibrin, or coagulated egg albumen) in an alkaline medium. If the filtrate of the duodenal contents be acid, a little of it may be neutralized and made slightly alkaline. To this or fibrin, a little of the white of a hard-boiled egg may be added, and the tube kept at body temperature for a few hours. If trypsin be present the fibrin or the white of egg will be digested and disappear. Erepsin is unable to digest fibrin, though it can digest casein, albumoses and peptones and all the polypeptids composed of neutral amino-acids.

Fuld's Method for Testing the Capacity to Digest Casein.—One gram of Grübler's pure casein is dissolved in one liter of 1 per cent solution of sodium carbonate and boiled. A few cubic centimeters of chloroform-toluol are added to preserve the solution. The filtered duodenal contents are diluted twenty times with an HCl solution made by mixing 30 c.c. of N/10-HCl with 70 c.c. water. The mixture is exactly neutralized with powdered soda, and, in a series of test tubes, definite amounts of this diluted juice are placed, 1.0-0.64-0.40-0.25 and 0.1 c.c. To each tube are added 2 c.c. of the casein solution. One control tube, free from duodenal juice, is also set up. Physiological salt solution is added to each of the tubes to the same volume, and the fluid in each made alkaline by the addition of a few drops of $\frac{N}{10}$-$NaHCO_3$. Each tube is shaken well and allowed to stand for half an hour at 37° C. A few drops of alcoholic solution of acetic acid (15 c.c. glacial acetic + 25 c.c. alcohol + 100 c.c. water) are added to each tube. In the tubes in which digestion has not taken place, a white ring will appear at the junction of the acid-alcohol with the casein solution.

Peptid Tests and Peptone Tests (Abderhalden) for Trypsin and Erepsin.—*Glycyl-l-tyrosin* is a dipeptid that is not split by stomach juice, but is quickly decomposed either by trypsin or erepsin into its components glycocoll and l-tyrosin. One can find out whether erepsin is present or not by using *glycyl-glycin,* which is split by erepsin, but not by trypsin. If erepsin be absent, then the splitting of glycyl-l-tyrosin by duodenal contents must be due to trypsin.

Silk peptone, or *peptone LaRoche,* can be used in place of glycyl-l-tyrosin. It is very rich in tyrosin, so that, when the peptone is split, tyrosin falls out of solution (Abderhalden and Schittenhelm). 0.5 gram silk-peptone is placed in 1 c.c. of the fluid to be examined. A few drops of concentrated solution of $NaHCO_3$ are added to make the mixture feebly alkaline. A little toluol is put in for preservation, and the mixture kept at 37° C. One looks from time to time for tyrosin crystals at the bottom. If trypsin be abundant, the tyrosin quickly falls out in beautiful crystals, visible to the naked eye, or on microscopical examination. Should no precipitate of tyrosin be found at the end of 48 hours, the mixture may be placed in the ice-box, when tyrosin may still fall out. If the solution remain clear, trypsin is absent.

The test may be used for quantitative work by weighing the tyrosin, or by centrifugalizing in calibrated tubes, or the change in the optical behavior of the mixture may be followed with the polarization apparatus (Optical Method of Abderhalden).

Test for Amylase (Pancreatic Diastase or Starch Splitting Ferment) in Duodenal Contents.—Starch appears to consist of two different sub-

stances, (1) starch proper, or amylose, which, on cleavage, yields maltose, and (2) another product, amylopektin, which, on cleavage, yields dextrose. An amylase in the pancreatic juice is the cause of this starch cleavage. The dextrines appear to be split by a dextrinase into maltose. The maltose from both sources is split by another ferment, maltase, into glucose.

For the **quantitative estimation of the diastatic ferment,** a method has been devised by J. Wohlgemuth. The method can be applied to duodenal contents or to the feces. Hawks' modification of it is described further on (See Examination of Feces). Wynhausen's modification of it suffices for clinical purposes and his test is as follows:

A filtrate of duodenal contents is placed in a series of test tubes, in diminishing quantities, and to each test tube is added 5 c.c. of a 1 per cent solution of soluble starch. The tubes are placed in the thermostat at 40° C. for 24 hours. A few drops of toluol are added to each tube for preservation, and the tubes plugged with cotton batting. At the end of the incubation period, each tube is filled to within a finger's breadth of the top with distilled water, and one drop of $\frac{N}{10}$ iodine solution added. A blue color will appear in the tubes in which starch is still present, and a red color in those in which erythrodextrin is present. The tubes containing only achroödextrin, maltose, or glucose will not be discolored. If, for example, 0.1 c.c. of filtrate digests 5 c.c. of starch solution, the diastase content, taking as a unit the fermentation of 1 c.c. of starch by 1 c.c. of filtrate, will be 50 units.

Test for Lipase (Steapsin) in Duodenal Contents.—A definite amount of aqueous solution of monobutyrin is placed in a series of test tubes, and a decreasing amount of the fluid to be examined added to each tube. After mixing, the tubes are allowed to stand in a water-bath at 37° C. for one hour, at the end of which time, phenolphthalein is added and the amount of acid present in each tube determined by titration with $\frac{N}{10}$ or $\frac{N}{100}$ NaOH.

The determinations of the proteolytic, amylolytic and fat splitting powers of the feces (*q. v.*) are far less valuable than similar determinations of duodenal contents.

iii. Abnormal Findings in Duodenal Contents

Either bile or pancreatic secretion may be absent. Absence of the duodenal reflex when gastric hyperchlorhydria exists points to hypersecretion of the pancreas or the duodenum (Kreuzfuchs). In yellow, bile containing duodenal secretion, it is usual to find all three pancreatic ferments present. In colorless, alkaline, duodenal juice, we may have

to deal with pancreatic secretion (all three ferments), with secretion from the duodenal wall alone (lipase), or with pyloric secretion (free from lipase). In ulcus duodeni, there is often hypersecretion of the duodenal wall (Matko, Bondi).

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F. Examination of the Feces

This should consist not simply of naked eye observation, but should include (1) a macroscopic, (2) a microscopic and (3) a chemical examination, preferably after the administration of the intestinal test-diet of Schmidt and Strasburger.

The normal feces vary in form, consistence, color and odor according to the food taken in. For this reason, it has been strongly recommended in abnormal cases to give a diet of known content for a period preceding the examination of the feces.

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1. The Intestinal Test Diet (Schmidt and Strasburger)

Two forms of test diet are made use of: (I) The Detailed Test Diet and (II) The General Test Diet.

(*a*) *The Detailed Test Diet*

Breakfast: 500 c. c. milk (or, if milk be badly borne, 500 c. c. of cocoa, made of 400 grams water, 20 grams cocoa, 10 grams sugar, and 100 grams milk); in addition, 50 grams of zwieback.

Forenoon: Half a liter oatmeal gruel, made of 40 grams oatmeal, 10 grams butter, 200 grams milk, 300 grams water, one egg, and a little salt, the whole to be passed through a sieve.

Mid-day: 125 grams hashed beef (weighed raw), broiled with 20 grams butter, as *rare* Hamburg steak; 250 grams purée of potato (made of 190 grams mashed potato, 100 grams of milk, 10 grams butter, and a little salt).

Afternoon: Same as breakfast.

Evening: Same as forenoon.

This test diet contains 102 grams protein, 111 grams fat, 191 grams carbohydrate, and corresponds to 2,234 calories. The test diet can be marked at its beginning, and at its end, by the administration of a tablet of 0.3 gram of finely powdered carmine in a conseal.

This diet is given for three days or longer, and the stool passed on the third day is examined. The whole stool is thoroughly mixed, and then a small piece of the homogeneous mass is rubbed up in a porcelain mortar with a little distilled water before the microscopic examination.

The advantage of such a standard diet for the clinical examination of the feces lies in the fact that only in this way is it possible to establish a normal standard, slight deviations from which can be easily recognized.

(*b*) *The General Test Diet*

For ambulant practice, Schmidt makes use of a general test diet, less rigid than the above, though satisfactory enough for ordinary diagnostic work.

Morning: $\frac{1}{2}$ liter of milk, or of tea or cocoa made with milk or water; 1 roll with butter; 1 soft egg.

Forenoon: 1 portion strained oatmeal, boiled with milk, with salt or sugar added if desired.

Noon: $\frac{1}{4}$ pound chopped lean beef, broiled on the outside with a little butter (raw inside); 1 portion purée of potato (passed through a fine sieve).

Afternoon: As in the morning, but no egg.

Evening: ½ liter milk, or 1 portion of soup; 1 roll with butter, and 1 or 2 soft eggs (or scrambled eggs).

In **pathological cases,** a change in the feces may be due (1) to *disturbances of gastric digestion,* especially from absence of pepsin and HCl (faulty digestion of connective tissue, and of the gluten framework of bread); (2) to *absence of bile* (disturbance of fat absorption); (3) to *insufficiency of pancreatic digestion* (faulty digestion of fats and proteins); (4) to *diminution of the ferments of the succus entericus;* (5) to *disturbances in the absorptive functions* rather than in faulty secretion; (6) to *increased secretion with simultaneously diminished absorption* (diarrhea); (7) to *pathological fermentations due to bacteria;* or (8) to certain *abnormal admixtures* with the feces (blood, pus, mucus, gallstones, parasites, including worms, amebae and pathological bacteria).

Reference

***Schmidt* (*E. A.*).** *The examination of the function of the intestines by means of the test diet, etc. (Transl. by C. D. Aaron.) Philadelphia, **1909,** F. A. Davis Co. 91 p. 8°.*

2. Macroscopic Examination of the Feces

Under this caption may be considered (1) the form and consistence, (2) the amount, (3) the color, (4) the odor, (5) the presence of gross residues of food, and (6) the presence of visible abnormal materials in the feces.

(*a*) *The Form and Consistence of Feces*

The form of the normal stool is cylindrical, and its consistence semisolid. If much cellulose be present, the stool looks spongy. In abnormal fermentations, the stool may be *frothy* (carbohydrates), or actually fluid (proteins). The stools in diarrhea may have a peculiar sediment ("rice-water stool" in cholera; "pea-soup stool" in typhoid). Dry scybala, showing the imprint of the haustra coli, indicate that the intestinal contents have remained an abnormally long time in the colon. Ribbonlike stools are met with in spastic constipation, and in intestinal stenosis.

(*b*) *The Amount of Feces*

This depends partly upon the food taken in, partly upon intestinal motility and digestion. On a vegetable diet, the stools are large and mixed with much undigested residue. On a meat diet, the residue is small, as most of the protein undergoes absorption. During fasting, the

feces become minimal in amount ("hunger feces"), and consist chiefly of residue of intestinal secretion, epithelial cells and bacteria.

Many small stools ("fractional defecation") are met with, sometimes, in nervous persons, sometimes, in intestinal stenosis.

Very bulky stools, after an ordinary diet, should excite the suspicion of pancreatic insufficiency (*q. v.*).

(*c*) *The Color of the Stools*

This depends, also, largely upon the character of the ingesta. Thus a meat diet yields dark brown stools; and a milk diet, yellow stools. Chocolate and cocoa, give a gray color; blackberries, a black color; bismuth, a black color; and calomel, a green color to the feces.

The clay-colored stool in biliary obstruction (acholic stools) depends partly on the absence of bile pigment, partly on the presence of undigested fat. Such fatty stools (steatorrhea) are sometimes met with in conditions other than jaundice; for example, in amyloid or tuberculous disease of the intestine, and especially in pancreatic insufficiency. In outspoken cases, the surface of the fatty stool may present a silver-gray appearance. Now and then the urobilin (hydrobilirubin) is present in the stool, in the form of a leukobase, and the stool may then simulate a fatty stool; but if the test for urobilin (*q. v.*) be made and be found positive, the true condition will be revealed.

In pancreatic steatorrhea, if the fat be extracted from a portion of the stool with ether, a brown color due to urobilin will appear.

(*d*) *The Odor of the Feces*

This is normally due chiefly to skatol, slightly to indol. The slower the passage of feces through the large intestine, the more pronounced the odor. In hypermotility (as in acute intestinal catarrh, dysentery, etc.), the feces may be odorless. In intestinal fermentative dyspepsia, there may be a sour odor, not unlike that of the stool of suckling babies. When food is imperfectly digested, the stool may have an offensive, sour odor. In amebic dysentery, the odor may resemble that of glue.

(*e*) *Food Residues in the Feces*

On careless eating, undigested masses may be visible in the feces (asparagus fiber; cellulose hulls of peas and beans; seeds; cherry-pits or plum-stones; bits of tendon, cartilage, bone, etc.).

To know whether normal food constituents (muscle fiber, fat, starch granules) are being properly digested or not, microscopical examination is essential.

(*f*) *Abnormal Constituents in the Feces Visible to the Naked Eye*

Blood, pus, mucus, stones, tissue fragments or parasites may be present.

Blood.—When visible to the naked eye, the appearance of blood in the feces varies according to its source. If the blood enter the intestine high up (as in gastric, or duodenal, ulcer, or in carcinoma) and the amount be not too large, it becomes intimately mixed with the feces and yields tarlike or chocolate-colored stools; if, however, the hemorrhage be a large one, or the passage through the canal be rapid (as in hemorrhage in typhoid), the blood may be but little altered.

In hemorrhages from the lower intestine (hemorrhoids, carcinoma recti, rectal polyp), the blood may be bright red and lie upon the surface of the formed feces. Blood from the colon may, however, be intimately mixed with the feces if these be fluid ("meat-juice" stools of dysentery).

Pus.—Pus occurs in small amounts in ulcerative processes in the large intestine (syphilis, dysentery, tuberculosis, etc.); while pus in larger amounts may be due to rupture, into the intestine, of abscesses (appendiceal, parametritic, periproctitic, etc.).

Mucus.—Mucus, in more than minimal amounts, points to intestinal catarrh. Mucus, with blood, is seen in dysentery. Sometimes, stools of pure mucus are passed, either in masses, or in the form of tubelike casts of the colon (colica mucosa, enteritis membranacea).

Stones or Concrements.—These are found by mixing the feces with water and rubbing through a sieve such as that of Einhorn or that of Boas. They may consist of gall-stones, pancreatic stones, or enteroliths.

Gall-stones.—Gall-stones are variable in size, and are usually recognizable by their polygonal, facetted form and smooth surface. They are yellow, brown, or grayish white in color, and are usually soft. On section, they are homogeneous, or show a nucleus; sometimes they are laminated. They consist sometimes of cholesterin, sometimes of calcium and bilirubin (See Chemical Analysis of Gall-stones). "False gall-stones" may be met with after attempted cures of gall-stones with olive oil!

Pancreatic Stones.—Pancreatic stones are rare; they consist usually of calcium carbonate.

True *enteroliths* are also rare, originating usually in the cecum. They have a central nucleus of organic substance (*e. g.*, a cherry-pit), upon which inorganic salts like ammoniomagnesium phosphate, or the sulphates of calcium and magnesium, have been deposited.

Occasionally, *plum-pits, cherry-pits, pear-cores, orange-pips,* or *fruit-pulp* may be met with.

Tissue Fragments.—Now and then, one finds carcinoma particles,

sloughing mucous membrane (dysentery), or pieces of necrotic intestine (invagination), or polyps detached from the sigmoid or the rectum.

Parasites.—The larger parasites (worms) may be visible to the naked eye. The intestinal parasites will be discussed in a subsequent section.

3. Microscopic Examination of the Feces

Technic.—A drop of a liquid stool may be examined directly on a glass slide. If the stool be solid, a small particle may be squeezed between the cover-glass and slide, and if necessary a drop of fluid added; or, better, a little of the solid stool may be rubbed up in a mortar with water, or with salt solution. In some instances, it is well to rub up a mass of the stool with fluid and collect the sediment by means of the centrifuge, repeating the process once or twice, before subjecting the sediment to microscopic examination.

In searching for the eggs of parasites (uncinaria, etc.), one may rub up a portion of the feces with a mixture of equal parts of concentrated HCl and ether, place in the centrifuge, and examine the sediment microscopically (Thelemann); or one may use salt solution or calcium chlorid solution of different strengths as a diluent (Bass). In this way, a sediment, or a scum, consisting almost entirely of uncinaria eggs is sometimes obtained.

On microscopic examination of the feces we look for (1) undigested food residues, (2) crystals, (3) cellular elements (leukocytes, epithelial cells, red blood corpuscles), (4) mucus, (5) bacteria, and (6) animal parasites or their eggs.

Undigested Food Residues.

These may consist of (1) muscle fibers, (2) connective tissue fibers, (3) fat droplets, or crystals, (4) starch granules, (5) plant cells, or (6) detritus.

As regards food constituents, a microscopic examination is of much more value, if made after the Schmidt-Strasburger test diet, than under other conditions. In Fig. 3, Pl. xvii, are shown the normal microscopic appearances after the test diet; in Fig. 4, Pl. xvii, are shown pathological constituents on a test diet.

It is well to add a drop of a 30 per cent acetic acid solution to one preparation, and to heat the specimen. This breaks up food masses, so that the fatty acids will appear as minute flakes through the specimen. To another preparation, Lugol's solution may be added; this gives a dark violet color to starch granules (potato residue) and also tints the muscle fibers, lime salts and yeast cells.

In normal digestion, the *remnants of muscle fibers* present show no distinct striation and no nuclei. If the nuclei be easily visible, there is probably pancreatic insufficiency. If *connective tissue* (white fibers or reticulum) be present in considerable amount, there has probably been faulty gastric digestion, since these tissues are digested only by pepsin

and hydrochloric acid and are not attacked by trypsin. *Starch granules* are never present in normal stools. When found they indicate faulty intestinal digestion. *Fat* in normal stools is present only in small amounts

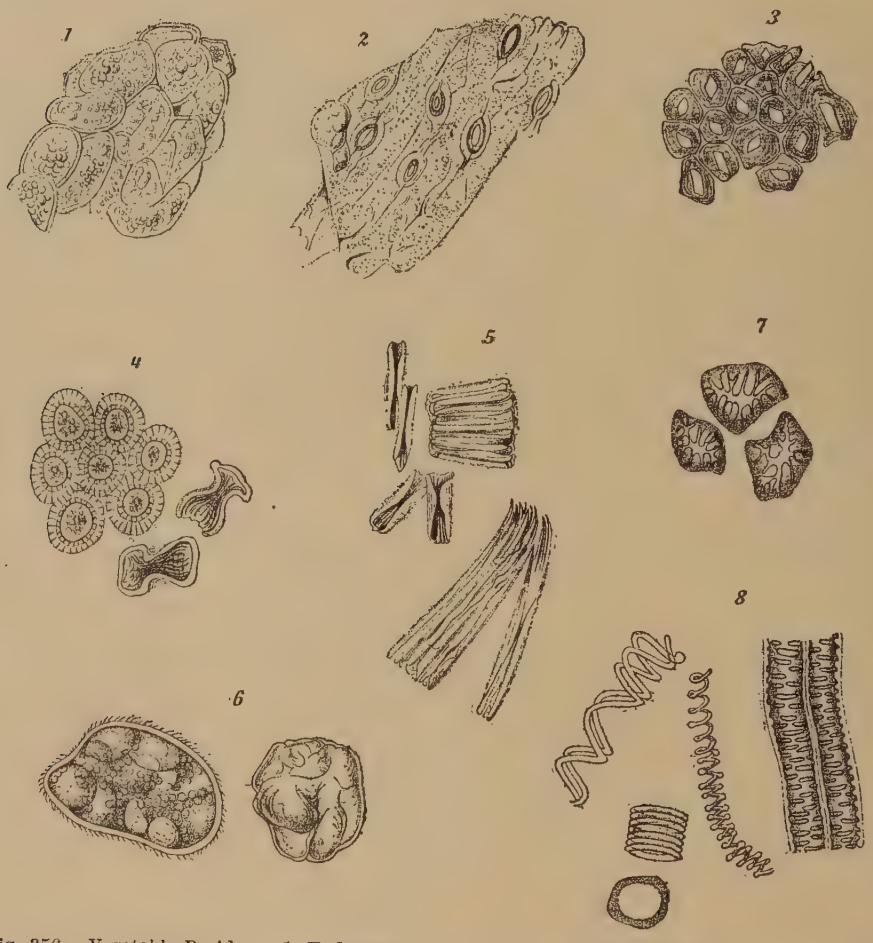

Fig. 356.—Vegetable Residues: 1. Endosperm from Rice; 2. Epidermis from Vegetable Leaves; 3. Crystal Cells from the Episperm. 4. Columnar Cells from the Episperm of Peas—Seen from Above and from the Side; 5. Palisade Layer (a) of Beans, (b) of Peas; 6. Parenchymatous Cell; 7. Stone Cells from Pears; 8. Different forms of Vessels and Their Remains. (After A. Schmidt and G. Strasburger, "Die Fäzes des Menschen," published by August Hirschwald, Berlin.)

in droplets and flakes. When present in larger amounts or when appearing as needles of the fatty acids or as soaps of lime and magnesium, a disturbance of fat absorption exists.

On ordinary diet, many kinds of *plant cells,* spiral fibers, membranes, etc., may be seen (Fig. 356).

Crystals.—Among those commonly met with may be mentioned the

Fig. 1.—Bismuth Crystals. (After N. v. Jagic u. H. K. Barrenschen, "Atlas u. Grund. d. Klin. d. Mikroskopie," published by M. Perles, Wien.)

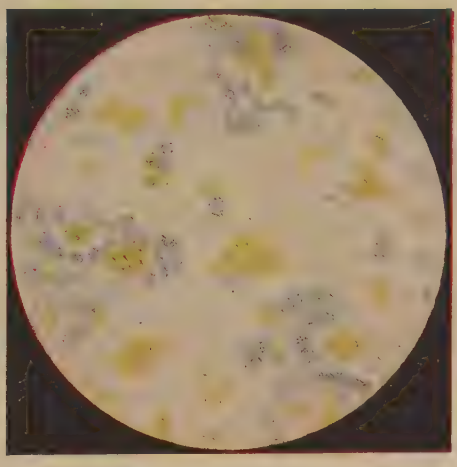

Fig. 2.—Blood and Pus in Stool. (After N. v. Jagic u. H. K. Barrenschen, "Atlas u. Grund. d. Klin. d. Mikroskopie," published by M. Perles, Wien.)

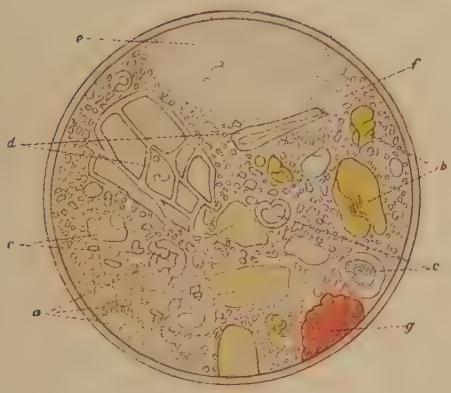

Fig. 3.—Composite Stool. Normal Constituents: (a) Muscle Fibers, (b) Yellow Lime Salts, (c) Soaps, (d) Vegetable Residue, (e) Empty Potato Cells, (f) Debris, (g) Remnants of Cocoa. (After A. Schmidt u. C. Strasburger, in "Die Fäzes des Menschen," published by A. Hirschwald, Berlin.)

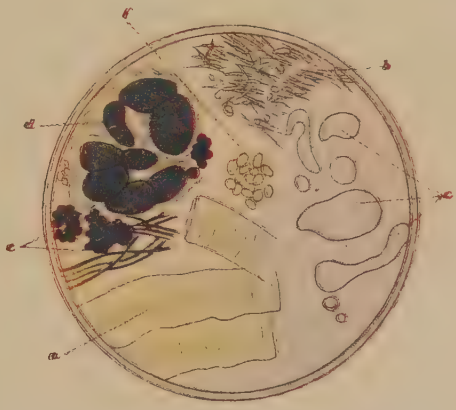

Fig. 4.—Composite Stool. Pathological Constituents: (a) Large Muscle Fibers, (b) Fatty Acid and Soap Needles (Crystals), (c) Neutral Fat, (d) Starch Granules in Potato Cells, (e) Bacteria Containing Granules, (f) Epithelial Cells. (After A. Schmidt u. C. Strasburger, in "Die Fäzes des Menschen," published by A. Hirschwald, Berlin.)

coffin-lid crystals of ammoniomagnesium phosphate, the flakelike masses of other lime salts, and occasionally octahedral Charcot-Leyden crystals. The latter may indicate helminthiasis, proctitis, or mucous colitis; they are often accompanied by eosinophilic leukocytes. Fatty acid crystals and soap crystals appear as needles or bundles of needles. The fatty acid crystals are soluble in ether and flow together on warming, but the soap crystals must first be heated with acetic acid before they show these properties.

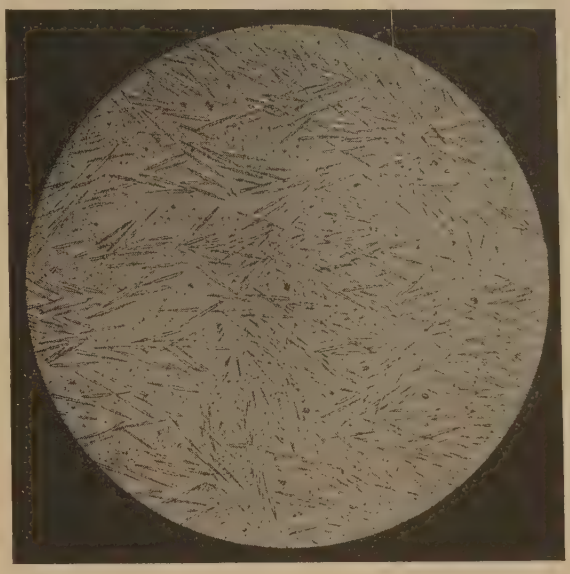

Fig. 357.—Fatty Acid Crystals. (After N. D. Jagic and H. K. Barrenscheen, "Atlas u. Grund. d. Klin. d. Mikroskopie," published by M. Perles, Wien.)

Envelope-shaped crystals of oxalate of lime may be found after a vegetable diet. Hematoidin crystals are rarely seen. After bismuth medication, small rhombic, brownish-black crystals of sulphate of bismuth become visible.

Cellular Elements.—In the stools we may find (1) *leukocytes,* in intestinal catarrh or ulcerations, many pus cells indicating ulcers or abscesses; *lymphocytes* are occasionally seen, and, sometimes, *eosinophils;* (2) *red blood corpuscles,* when found, usually indicate rectal hemorrhages (hemorrhoids); after hemorrhage higher up, the red corpuscles are usually destroyed, though shadows may be visible, and we depend upon chemical tests (*q. v.*) for the recognition of blood; (3) single *epithelial cells* are common, larger numbers pointing to catarrhal inflammation; the epithelium is usually cylindrical, though squamous epithelium may come from the anus.

Mucus.—Cellular elements may be enclosed in mucus, which shows, microscopically, delicate contours penetrated by fine, irregular lines running in parallel groups and made more distinct by the addition of acetic acid.

Bacteria.—Microörganisms are always present in enormous numbers in the feces. For purposes of diagnosis, tests for tubercle bacilli, typhoid bacilli, paratyphoid bacilli and cholera bacilli may be helpful. Tubercle bacilli may sometimes be demonstrated by the carbol-fuchsin method; for

typhoid, paratyphoid, dysentery, and cholera bacilli cultural methods are necessary. (See Section on Infectious Diseases.)

In looking for *tubercle bacilli,* one rubs up a piece of feces, the size of a bean, with 30 c.c. of water and centrifugalizes. The upper third of the fluid is pipetted off and mixed with twice its volume of 95 per cent alcohol and again centrifugalized. The sediment is placed on a glass slide, dried, fixed, and stained by the ordinary Ziehl-Neelsen method (*q. v.*).

Parasites.—In searching for amebae and other protozoon parasites, the formed stool (*not* after purgation) should be examined fresh, while still warm, and, preferably, upon a warm stage. It is often well to pass a rectal tube; one can sometimes secure a bit of bloody mucus containing parasites in the eye of the tube.

The specimen may be examined on an ordinary glass slide, under a cover-glass, or in a hanging drop.

Entamebae

The motility should be observed. The differentiation of ectoplasm and endoplasm is helpful, as is also the observation of phagocytosis of red blood corpuscles. Encysted forms should be looked for.

Permanent preparations may be made by fixing a smear on a cover-slip, laying the cover-slip for a few seconds in a fixing mixture (100 c.c. saturated aqueous solution of corrosive sublimate + 50 c.c. absolute alcohol + 5 drops glacial acetic acid), then washing for half an hour in 60 per cent iodin alcohol, then in 70 per cent alcohol, and, finally, in distilled water. The specimen is then stained for half an hour in borax carmine, and washed in acid alcohol (0.1 per cent HCl, plus 70 per cent alcohol) until clouds of color cease to be given off; it is then counter-stained with Lichtgrun, dehydrated (through graded alcohols to absolute alcohol), cleared in xylol and cedar oil, and mounted.

Fig. 358.—Entameba histolytica in Feces.

Walker's technic for studying the *nuclear characteristics of human amebae* can be warmly recommended: Fixation of thin moist smear in sublimate alcohol (1 part of absolute alcohol + 2 parts saturated aqueous solution sublimate) for 10-15 minutes; wash well in H_2O; stain in alum hemotoxylin for 5 minutes.

Vegetative amebae can be well demonstrated by vital staining; an emulsion of the feces is tinged with a 1 per cent aqueous solution of neutral red (E. R. Stitt).

Encysted amebae should be looked for

in two ways: (1) by emulsifying feces in Gram's iodin solution, in which **Entameba coli** with its 8 nuclei stands out well; and (2) by the sublimate-fixation of smears and alum-hematoxylin stain above described, in which the 4 nuclei and the "chromidial bodies" of **Entameba histolytica (gen. tetragena)** are well shown. In looking for encysted amebae in feces, a $\frac{2}{3}$ in. objective is advantageous (Walker). Formerly, we made reports on mobile amebae only, when studying feces for pathogenic amebae; now, we know that the differential diagnosis between pathogenic and non-pathogenic amebae is best made from the observation of non-mobile encysted forms.

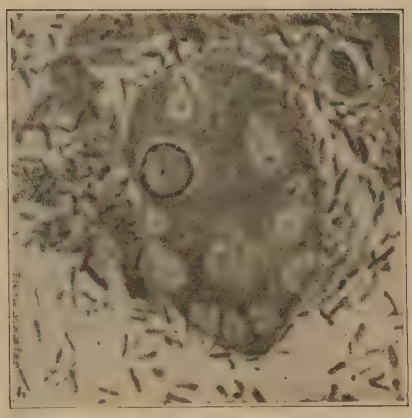

Fig. 359.—Entameba histolytica in Feces. Note the Chromatin-poor Nucleus with Beading at Its Periphery. A Number of Laked Red Corpuscles Are Visible in the Protoplasm Zenker Fixation; Alum Hematoxylin. (After Baetjer and Sellards, J. H. H. Bull.)

Walker's Table for Differentiating Entamebae

Mobile Stage

A. Entameba histolytica.	B. Entameba coli.
1. Appearance hyaline.	1. Appearance porcelaneous.
2. Refractiveness more feeble.	2. Refractiveness more pronounced.
3. Movements active in the fresh stool.	3. Movements sluggish.
4. Nucleus more or less indistinct.	4. Nucleus distinct.
5. Chromatin of nucleus scanty.	5. Chromatin of nucleus abundant.

Encysted Stage

A. Entameba histolytica.	B. Entameba coli.
1. Cyst smaller.	1. Cyst larger.
2. Cyst less refractive.	2. Cyst more refractive.
3. Cyst usually contains elongated refraction bodies known as "chromidial bodies."	3. Cysts do not contain "chromidial bodies."
4. Nuclei never more than 4.	4. Nuclei 8, occasionally more.
5. Cyst wall thinner.	5. Cyst wall thicker.

Cercomonas hominis

This actively mobile flagellate is pear-shaped, pointed posteriorly, 0.010 to 0.012 mm. long; at the anterior, rounded end is a single flagellum. Nucleus, near anterior end.

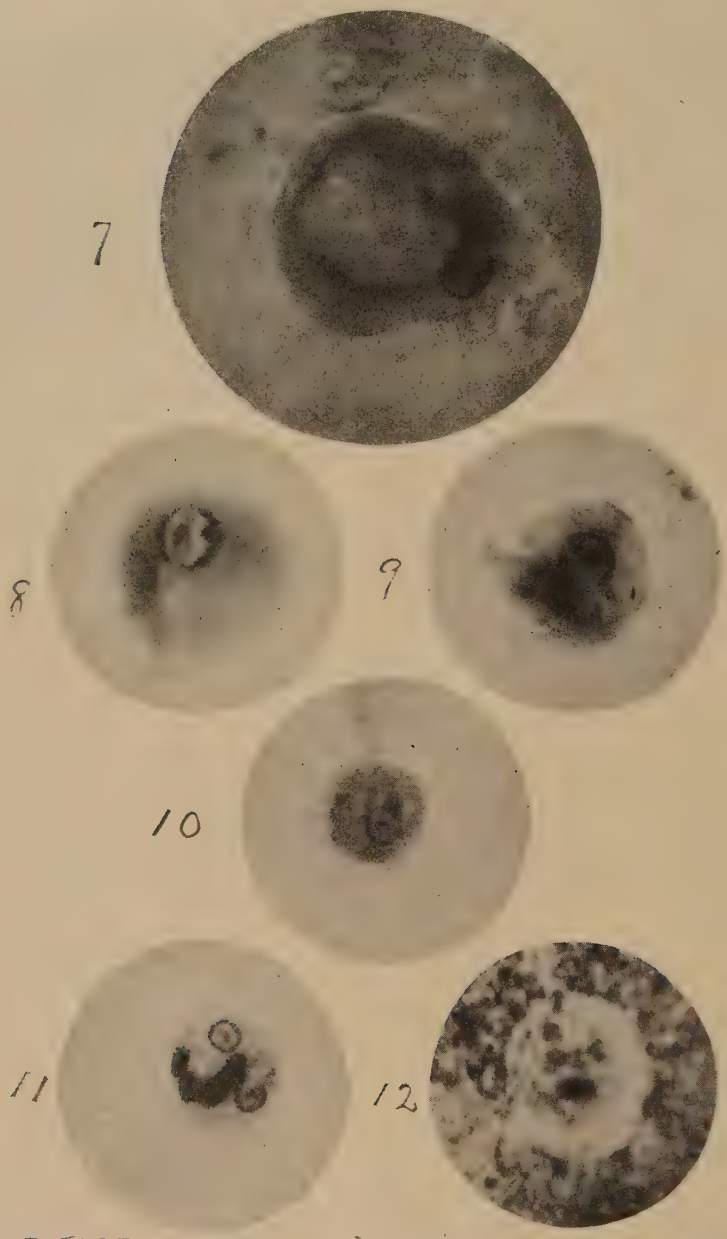

Fig. 360.—Encysted Forms of Entamebae: 7. Very Large Cyst of E. coli, Showing the Large Vacuole That Is Frequently Present in the Cysts Before the Primary Division of the Nucleus. Note the Spindle-shaped Karyosome Which Is Frequently Observed Just Prior to the Division of This Portion of the Nucleus; × 1,200; 8. Young Cysts of E. coli, Showing Division of the Karyosome and the Thick Nuclear Membrane; x 1,200; 9. Precystic Form of E. coli. Note Reduction in Size and the Elongation of the Karyosome Prior to Division; × 1,200; 10. Early Cystic Stage of E. histolytica, Showing Small Size and Typical Nucleus; × 1,150; 11. Encysted Form of E. histolytica, Showing the Division of the Primary Nucleus Into Two Nuclei; also the Large Chromididial Masses Characteristic of This Species; × 1,150: 12. Encysted Form of E. histolytica, Showing the Four Daughter Nuclei Characteristic of the Fully Developed Cyst; Also a Large Chromidial Body; x 1,150. (After C. F. Craig, Arch. Int. Med.)

Trichomonas intestinalis

This extremely motile flagellate is pear-shaped, pointed posteriorly, averaging 0.017 mm. in length, and 0.010 mm. in width; at the anterior, rounded end are

Fig. 361.—Trichomonas intestinalis. (After Grassi in M. Braun's "Die thierischen Parasiten des Menschen," published by Bale Sons & Danielsson, London.)

four flagella; an undulating membrane extends from the site of insertion of the flagella to the posterior end. The body is refractive, and of greenish tint. Encysted forms occur. Slightly, if at all, pathogenic.

Lamblia intestinalis

This motile flagellate is pear-shaped, pointed posteriorly, 0.010 to 0.021 mm. long, 0.005 to 0.012 mm. broad; near its anterior extremity is a cuplike depression by which it attaches itself to the intestinal mucosa. It has 8 flagella, arranged in

Fig. 362.—Lamblia intestinalis from the Surface, from the Side, on Intestinal Epithelium, Dead, and Encysted. (After M. Braun, "Die thierischen Parasiten des Menschen," published by Bale Sons & Danielsson, London.)

pairs, three pairs at the edge of the cuplike depression, one pair at the posterior extremity of the parasite. Protoplasm, finely granular; nucleus, beneath cuplike depression. Encysted forms occur. Non-pathogenic.

Balantidium coli

This infusorian parasite is oval, 0.060 to 0.1 mm. long, 0.05 to 0.07 broad. Anterior end blunter than posterior. Funnel-shaped peristome anteriorly; cilia

on surface of parasite and around peristome. Ectosarc clear; endosarc granular; 2 or more contractile vacuoles in endosarc. Macronucleus, crescentic; micronu-

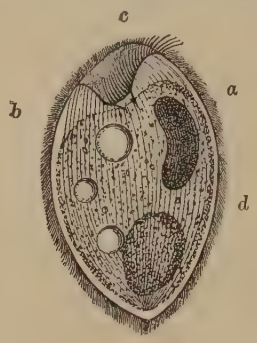

Fig. 363.—Balantidium coli: (*a*) Nucleus; (*b*) Vacuole; (*c*) Peristome; (*d*) Nutrient Particles. After Leuckart in M. Braun's "Die thierischen Parasiten des Menschen," published by Bale Sons & Danielsson, London.)

cleus, round, posterior. Encysted forms occur. This parasite can set up a severe ulcerative colitis, not unlike amebic dysentery (Strong, Bowman). I have seen one case, with obstinate diarrhea and severe anemia; there were an enormous number of the parasites in the feces.

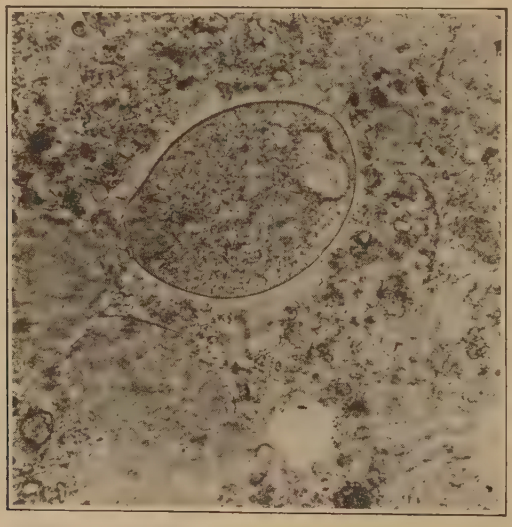

Fig. 364.—Balantidium coli in Fresh Feces. (After W. G. MacCarty, Surg., Gynecol. and Obstet.)

The **larger intestinal parasites,** including the worms and their eggs, are described further on.

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4. Chemical Examination of the Feces

This includes a study of the reaction, tests for the presence of blood, urobilin, bilirubin, protein, undigested carbohydrates, and fat, the analysis of stones, and tests for ferments.

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(*a*) *Reaction of the Feces*

This is tested with blue and red litmus paper. Neutral or feebly alkaline, normally, the stools may, in carbohydrate fermentation, become acid. If there be marked putrefaction of protein within the intestine, the reaction may become markedly alkaline. Alkaline stools contain free ammonia; this ammonia-content and its relations to fermentation have been studied by H. Fischer.

(*b*) *Chemical Tests for Blood, or Blood Pigment, in Stools*

Caution: The test is of no value unless meat (including sausage) have been excluded from the food for several days (at least two or three), before the test.

The tests for blood in the stools, especially for **occult blood**, are of great importance. They are often positive, when the presence of blood is wholly unsuspected on naked-eye examination. The feces may contain as much as 5 per cent of blood without change in the naked-eye appearance. The recognition of minute hemorrhages, especially of minimal hemorrhages (occult blood) is of the greatest value in the diagnosis of ulcer and carcinoma of the stomach and of the duodenum, and as a clue to the existence of helminthiasis.

Several very delicate tests are available; the more important of these will be here described; namely, (1) Weber's test, (2) the spectroscopic method, (3) Schumm's modification of Weber's test, (4) Rossel's test, and (5) the benzidin test.

(1) **Weber's Test.**—*Principle:* The blood pigment in the feces is converted into acid hematin by treatment with glacial acetic acid; this is extracted with ether, and yields a bluish violet color on the addition of Van Deen's reagent (tincture of guaiac and old, ozonized terpentine).

Technic.—One rubs up feces with a mixture of two parts water and one part glacial acetic acid, and shakes with ether. The acid-ether extract is allowed to separate. If it be not clear after a few minutes, a few drops of alcohol are added. If the ether be untinted, blood is absent, but if it be tinted reddish brown, either acid hematin, or some pigment resembling it, is present. To make sure whether the color depends upon hematin, or on some other pigment, we apply the guaiac test. A few cubic centimeters of the extract are poured into a test tube and mixed with 10 drops of freshly prepared tincture of guaiac (0.5 g. guaiac resin, shaken with 3 c. cm. alcohol) and 20 to 30 drops of old oil of turpentine, or the same amount of hydrogen peroxid solution. The mixture is well shaken. The appearance, immediately, or within a few minutes, of an outspoken blue, or violet, color, which fades on standing, speaks strongly for the presence of blood pigment, while if blood pigment be absent, the color remains reddish brown, or may assume a greenish tint.

A convenient way to apply the test is to deposit a few drops of the extract of feces in the center of a circular piece of white filter paper on a plate. A few drops of tincture of guaiac are added to the moistened spot, and then a few drops of H_2O_2 solution. A positive reaction is indicated by waves of blue color extending out into the moistened filter paper.

This guaiac test is very delicate and if the result be negative, the absence of blood is certain. But a positive reaction may be yielded by many substances other than blood (for the sources of error, see Kastle's article, 1909). As a control, we resort to the spectroscopic test.

(2) **Spectroscopic Test.**—A second part of the ether extract prepared for Weber's test may be made alkaline by the addition of ammonia, after which a few drops of a solution of ammonium sulphide are added; the specimen is then examined spectroscopically. If the spectrum of reduced hematin (see spectrum table), or at least its first band in the yellow-green, be present, blood pigment is certainly present. If no blue color appear with the guaiac-turpentine test, the presence of blood is ruled out, and the spectroscopic control is superfluous. For methods of Spectroscopy see Part VII.

(3) **Schumm's Modification of Weber's Test.**—By this method, pigments other than blood pigment, fatty acids, and water, are removed by a preliminary treatment with alcohol and ether.

In solid stools, a piece the size of a small walnut (4 grams) is rubbed up with 30 c.c. of a mixture of equal parts of alcohol and ether, and filtered. The residue on the filter is washed with more of the alcohol-ether mixture, being gently stirred at the same time with a glass rod. After the washings have passed through, the residue is again washed twice with pure ether, under gentle stirring. This residue, which contains the blood pigment, is next treated, on the same filter, with 4 c.c. of glacial acetic acid and the filtrate collected as it passes through, filtration being hastened by gentle stirring with a glass rod. When the filtration is nearly done, another 4 c.c. of glacial acetic acid is poured on and similarly mixed. The acid filtrate is next poured upon the filter and stirred with the sediment. Several cubic centimeters of this final filtrate are diluted with two or three parts of ether and the fluid thus obtained mixed with half its volume of distilled water and thoroughly shaken. If separation do not take place, a little alcohol is added. After separation, the ethereal extract is again shaken up with a little water. A part of the ethereal extract thus obtained is placed in a clean, dry, test tube and a mixture of ten drops of guaiac tincture and twenty drops of turpentine oil added. If hematin be present, a violet, bluish violet, reddish violet, or greenish blue color gradually appears.

If the stools be thin, a larger amount is taken and rubbed up with four volumes of alcohol-ether. If the stool be acid, it is first neutralized with a few drops of concentrated NaOH.

The same method can be used for testing for occult blood in stomach contents, provided they be first neutralized with NaOH, as HCl interferes with the reaction.

(4) **Rossel's Aloin Test.**—For this test, the acid-ether extract is made as in Weber's test, and to it are added first 20-40 drops of old oil of turpentine (or of H_2O_2 solution), and then 15-30 drops of a freshly prepared aloin solution (as much aloin as goes on the point of a knife, mixed with 3-5 c.c. of 70 per cent alcohol just before using). If hematin be present, a light red color quickly appears, which on standing becomes cherry red. If no blood be present, the aloin solution remains yellow and is reddened only slightly after one or two hours.

(5) **Benzidin Test.**—A small piece of the feces is rubbed up with water; 3 c.c. of this unfiltered suspension is mixed with 2 c.c. of an alcoholic benzidin

solution (concentrated by heat and filtered after cooling) and 2 c.c. of a 3 per cent solution of peroxid of hydrogen; a few drops of acetic acid are then added. If blood be present, an intense green color appears. The *moist-filter-paper* method, used for the guaiac test, may also be applied in making the benzidin-test.

The *benzidin paper* introduced by Max Einhorn is very convenient for quick orientation; a strip of the paper is dipped in the fluid suspected to contain blood pigment, and a little hydrogen peroxid sprinkled over the paper thus moistened. If blood be present, the paper turns green. The test is extremely delicate, but it is open to error from several sources. A negative result is, however, of distinct value.

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(c) Tests for Urobilin or Hydrobilirubin in the Feces

The bile pigment is changed in the intestine to *hydrobilirubin* (identical with *urobilin*). Most of this is given out in the feces, but some is absorbed and given out as urobilin in the urine.

The conversion of bilirubin into hydrobilirubin occurs chiefly in the cecum and the ascending colon. Sometimes, reduction goes beyond the hydrobilirubin stage to the colorless leukobase known as *leukohydrobilirubin,* or *urobilinogen.* Unchanged bilirubin appears in the stools only when putrefactive processes are absent (meconium) or when there is insufficient reduction, due to increased peristalsis. Occasionally, *biliverdin,* the first oxidation product of bilirubin, appears in the feces.

Zinc Chlorid Test.—A portion of feces is rubbed up with alcohol containing a little sulphuric acid; this acid extract is concentrated at 40-50° C. to a small volume. It is then shaken up with chloroform, and to the chloroform extract, a few drops of concentrated alcoholic solution of zinc chlorid are added. On filtration, if hydrobilirubin be present, a beautiful green fluorescence appears in the filtrate. This filtrate also shows characteristic absorption bands (between the green and the blue) on spectroscopic examination (See Spectrum Table). Or, fresh feces, in watery suspension, may be acidulated with acetic acid, extracted with amyl alcohol, and the extract examined spectroscopically.

Zinc Acetate Test (Schlesinger).—To a little of the acid-chloroform extract above, neutralized with ammonia, add an equal volume of a saturated solution of zinc acetate in absolute alcohol. After shaking, add a few drops of Lugol's solution and filter. Fluorescence of the filtrate indicates the presence of urobilin.

Sublimate Test (Schmidt).—A portion of fresh feces (size of a hazel-nut) is rubbed up in a mortar with three times its volume of a saturated aqueous solution of corrosive sublimate. This is allowed to stand in a watch-glass, or, better, in an uncovered Petri dish, for twenty-four hours at the room temperature, or for ½ to 1 hour in the thermostat. If hydrobilirubin be present, the particles containing it will assume a red color, while particles containing bilirubin will be colored green. The colors can be well seen in small particles under the microscope.

Test for Urobilinogen.—To test for the leukobase (urobilinogen) in the feces, indol and skatol are first removed by rubbing up with ligroin. The residue is extracted with alcohol. To 5 c. cm. of this filtered extract, 5-10 drops of a 2 per cent solution of p-dimethylaminobenzaldehyd (1 gram in 50 grams HCl and 50 grams water) are added. A cherry red color appears in the cold, or on heating (Ehrlich's "aldehyde reaction").

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(*d*) *Test for Bilirubin in the Feces* (*Huppert*)

A portion of feces is rubbed up with water, mixed with milk of lime, and filtered. The residue is then placed in a test tube, covered with acid alcohol (HCl), and boiled for some time. The fluid turns green if bilirubin be present; or Schmidt's sublimate test, described above, may be used.

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(*e*) *Test for Protein in the Feces*

This is sometimes present in the stools in diarrhea, especially in ulcerative processes (typhoid fever). The normal feces are free from protein. To demon-

strate its presence, the feces are extracted with water, and acidulated with acetic acid; this extract is filtered, and a portion of it heated in a test tube, just as in testing for albumin in the urine. If protein be present, it will be precipitated.

(*f*) *Test for Undigested Carbohydrates in the Feces*

When digestion in the small intestine is impaired, undigested carbohydrates may appear in the feces. If this be suspected, the test-diet of Schmidt-Strassburger should be given (see above). The feces after this diet should be free from carbohydrates, but in intestinal fermentative dyspepsia, they may still be present, when they may be demonstrated by the following test:

Schmidt's Thermostat-Fermentation Test.—For this test, Schmidt's fermentation tube is convenient. A portion of feces is rubbed up with water and about 5 grams of the mixture placed in a fermentation tube. The perforated rubber cork is put in, care being taken to see that no air bubbles remain in the fermentation tube over the feces. Above this fermentation tube, a calibrated tube, filled with water, and communicating with a third empty tube, is placed. If gases are developed in the fermentation tube, they will rise and displace the water from one tube into the other; from the amount of gas produced, the degree of fermentation may be estimated. The tube is placed in the thermostat for 24 hours to ferment.

Instead of Schmidt's tube, the ordinary fermentation tube of the bacteriological laboratories may be employed.

If more than ⅓ of the tube be filled with gas the fermentation exceeds the amount to be expected of a normal stool.

If there be fermentation of carbohydrates going on, the feces will become acid in reaction and lighter in color; if protein putrefaction go on, the reaction will become alkaline and the color darker, and a foul odor will appear. In the latter case, the putrefaction will most probably be found to be due to mucus, blood, pus, or transuded serum, mixed with the stool.

This fermentation test is of real diagnostic value in the recognition of the so-called **fermentative-dyspepsia**, in which the stools are voluminous and frothy, and often contain yeast cells, visible under the microscope.

Slight fermentation may occur in a normal stool; only outspoken fermentations are of diagnostic value.

(*g*) *Tests for Fat in the Feces*

A good microchemical test for fat in feces is to treat one preparation with osmic acid, which turns fats containing oleic acid black, and another preparation with Sudan red, which stains all neutral fats red. Fat may be determined quantitatively by the methods used for the blood (See Section VII). Perhaps the best method, however, is the new one of Folin and Wentworth, the technic of which is fully described in their publication.

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(*h*) *Analysis of Stones Obtained from the Feces*

Gall-Stones.—On testing for bile pigments, solvents like alcohol, glacial acetic acid, and chloroform should be used in large excess, in water, to insure easy filtration; the filtrate is subsequently concentrated to a small volume. Some stones consist of pure cholesterin, some of cholesterin and bilirubin combined with calcium.

For chemical examination, the stone is powdered, washed with boiling water to remove bile, and filtered. The powder, after being thus purified and dried, is extracted with equal parts of warm alcohol and ether, the residue being washed with the filtrate. The filtrate is then concentrated, when cholesterin crystalizes out in rhombic plates. The cholesterin can be dissolved in chloroform and mixed with concentrated H_2SO_4, when a cherry red color appears, which changes to blue and green.

The residue of the powdered stone is treated with HCl; if $CaCO_3$ be present effervescence occurs.

Filter and wash with water. Evaporate the filtrate to dryness and test for inorganic constituents. In order to demonstrate bilirubin in a stone, we extract with hot chloroform, and mix with fuming nitric acid (Gmelin's test).

Enteroliths.—These consist of ammonium-magnesium phosphate and calcium phosphate. The tests are the same as for urinary calculi (*q. v.*). Intestinal "sand" may be composed of the same substances; sometimes it consists of materials taken in with the food or with drugs (magnesium carbonate, phosphates, salol, bismuth compounds, etc.).

Pancreatic Stones.—These consist of carbonate and phosphate of lime, deposited upon an organic nucleus. The lime salts can be dissolved off with HCl, leaving the organic substance behind.

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(*i*) *Tests for Ferments in the Feces*

A study of the feces for ferments has some clinical value, though far less than the study of the enzymes in the duodenal contents (already described). Trypsin and amylase are the two enzymes most often looked for.

Test for Trypsin in Feces.—A watery suspension of feces is extracted with glycerin. To 10 c.c. of 0.4 per cent solution Na_2CO_3, one adds 1-2 c.c. of the glycerin extract, and sets up a digestion experiment at 37° C. with fibrin (stained in carmine). A little toluol is added to prevent bacterial growth. Another method, that of O. Gross, makes use of casein and sodium carbonate; for the details of this method, the original article, or the epitome of it, given in R. Morris's Clinical Laboratory Methods, should be consulted. Fuld's method, as described under examination of duodenal contents, may also be used.

Test for Amylase in Feces.—The best method is Hawk's modification of Wohlgemuth's method. To 2 g. of fresh feces, accurately weighed, are added 8 c.c. of a phosphate chlorid solution (0.1 molecules di-hydrogen sodium phosphate and 0.2 molecule di-sodium hydrogen phosphate per liter of 1 per cent solution of sodium chlorid); 2 c.c. are added at a time, the mixture of feces and fluid being rubbed thoroughly in a mortar after each addition of the extraction medium. The neutral suspension thus formed is kept at room temperature for half an hour, and frequently stirred. It is then placed in a graduated 15 c.c. centrifuge tube, the mortar and pestle being washed carefully with the phosphate-chlorid solution and the washings added. The centrifuge tube is then filled up to the 15 c.c. mark with phosphate-chlorid solution, and centrifugalized (15 minutes, or longer) to thorough sedimentation. The height of the column of sediment is read and recorded; let us say, for example, it is 6.2 c.c.

The supernatant liquid is transferred, by means of a bent pipet, to a 50 c.c. volumetric flash and diluted to the 50 c.c. mark with phosphate-chlorid solution, mixing thoroughly. The amylolytic activity of this extract is then determined.

In a series of six graduated tubes, volumes of the extract ranging from 2.5 to 0.078 c.c., are added, so that each successive tube in the series contains half as much as the preceding tube. The quantity of fluid in each tube is then made up to 2.5 c.c. by the addition of phosphate-chlorid solution; thus uniformity in the concentration of electrolytes is secured.

To each tube are now added 5 c.c. of a starch solution (1 per cent) and 3 drops of toluol. The tubes are well shaken, stoppered, and incubated at 37° C. for 24 hours.

Each tube is then filled to within half an inch of the top with ice-water, one drop of $\frac{N}{10}$ iodin solution added, the tubes shaken, and carefully examined in a strong light.

The last tube in the series that shows entire absence of color owing to the complete transformation of its starch into dextrin and sugar will be the dilution on which to base the calculation of the amylolytic activity (Df). This may be expressed in terms of 1 c.c. of *sediment* obtained by centrifugalization as above described. Thus if the tube containing 0.31 c.c. of the phosphate-chlorid extract transformed the 5 c.c. of starch solution added, the amylolytic power for 1 c.c. of this extract would be $\frac{1.0}{0.31} \times 5 = 16.1$ c.c.

But 50 c.c. of extract was obtained from 6.2 c.c. of sediment, that is 1 c.c. of sediment corresponds to $\frac{50}{6.2} = 8$ c.c. of extract. The amylolytic value of 1 c.c. of sediment is therefore $16.1 \times 8 = 128.8$.

The activity is expressed thus:

$$Df\frac{38°}{24 \text{ hrs.}} = 128.8.$$

The average value for normal feces is 150.

Test for Maltase in Feces.—One tests for the enzyme maltase by mixing the aqueous fecal extract with a solution of maltose, and observes whether cleavage takes place or not (polarimetry, osazon test).

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(*j*) *Schematic View of the Findings in the Feces in the more Important Diseases of the Digestive Tract (After W. Wolff)*

1. *Gastrogenous intestinal disturbances*	= Connective tissue residues.
2. *Gastroenteritis*	= Meat residues.
3. *Catarrh of the small intestine*	= Meat and starch residues; carbohydrate fermentation test positive; very fine flocculi of mucus with green color with the sublimate test.
4. *Pancreatic diseases*	= Fatty stools.
5. *Obstruction to bile duct*	= Fatty stool; negative sublimate test; negative benzaldehyde reaction.
6. *Catarrh of large intestine*	= Coarser masses of mucus; red color with sublimate test; digestion not much disturbed.
7. *Ulcerations*	= Putrefaction of protein; red and white blood corpuscles; occult blood.

G. Intestinal Parasites, Especially Worms and their Eggs

The protozoan parasites have been mentioned under microscopic examination of the feces. Here we shall take up the metazoan parasites (and their eggs) encountered in the feces.

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1. The Search for Parasites and Eggs

Many *worms*, not all, are visible to the naked eye. To make sure that they be not overlooked, the whole stool should be thinned with water, and passed through a sieve. *Eggs* are found on microscopical examination of the stools, or in the sediment obtained after suspension and centrifugalization.

Eosinophilia in the blood, and the presence of Charcot-Leyden crystals in the stool, always lead us to search for intestinal parasites, though both phenomena may be due to trichiniasis, to bronchial asthma, or to certain skin lesions. Occult blood in the stool should make one think of the possibility of helminthiasis as a cause.

In looking for *Oxyuris*, a glass rod may be introduced into the anus and the particle of stool obtained examined. In some cases, especially if there be excoriations about the anus, a scraping of the part will yield a portion of the body of a worm, containing the ova. If *Ascaris* be suspected,

the stool may be examined after a brisk purge. *Tapeworms* may be suspected if patients complain of an enormous appetite; usually, however, the patient's attention is first called to the invasion by observing segments in the feces.

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2. General Classification of the Worms

Worms are bilaterally symmetrical animals, the bodies of which are generally divided into a number of similar segments. They are always devoid of articulated limbs. The following is a general classification of the worms:

(A) Worms that have no ventral nervous chain.
  I. With no ciliated prebuccal apparatus.
    1. Flat body = **Plathelminthes.**
    2. Cylindrical body = **Nemathelminthes.**
  II. With ciliated prebuccal apparatus = **Rotifera, Bryozoa and Brachiopoda.**

(B) Worms that have a ventral nervous chain = **Annelids.**

For medicine, the flat worms, or plathelminthes (including the tapeworms or cestodes and the trematodes), the round worms or nemathelminthes (including especially the nematodes), and the annelids, or leeches, are of interest.

The feces may contain (1) portions of tapeworms or cestodes, (2) trematodes, (3) round worms or nematodes, or (4) the eggs of any of these.

3. The Tapeworms (Cestodes)

(*a*) *General Characters*

The *Cestodes* form one of the five orders of *Plathelminthes*. It is a parasitic order; the body is naked in the adult state; there is no digestive tube; and the body is segmented.

These cestodes consist of ribbonlike animal colonies made up of a head, or suction apparatus (*scolex*), by which they attach themselves to the intestinal wall, a non-segmented *neck*, and a longer or shorter trunk, like a ribbon or chain (*strobila*) made up of single individuals, in the form of flat segments (*proglottides*), which arise by budding. As long as the

Taenia saginata

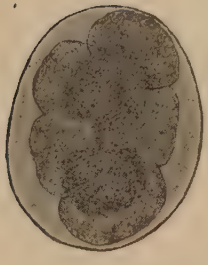
Hymenolepis nana

Hymenolepis diminuta

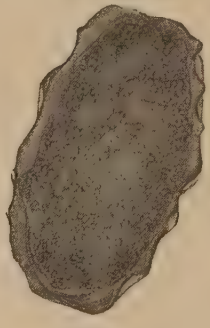
Dibothriocephalus latus

Trichiurus trichiura

Oxyuris vermicularis



Necator americanus



Ascaris lumbricoides
(unfertilized)

Ascaris lumbricoides
(containing embryo)

Fig. 365.—Ova in Human Feces. (Drawn to Scale.)

head is present, new segments can be continuously formed while the hindmost ones are thrown off in the feces. The older segments, unlike the newly formed ones, have mature *sexual organs*, the openings of which may be placed laterally (as in tenia) or in the middle line (as in dibothriocephalus). Each segment is bisexual and may contain thousands of eggs. Should these eggs reach the stomach of an intermediate host (pig, ox, fish, etc.) they develop into embryos, which bore through the intestinal wall, and, reaching the blood stream, are distributed in the organs of the animal. There, the embryo develops into a vesicle, which propagates itself by budding. Each bud, containing the rudiment of a scolex, is called a *cysticercus*. Should such a body be swallowed in infected meat (*e. g.*, measly pork in

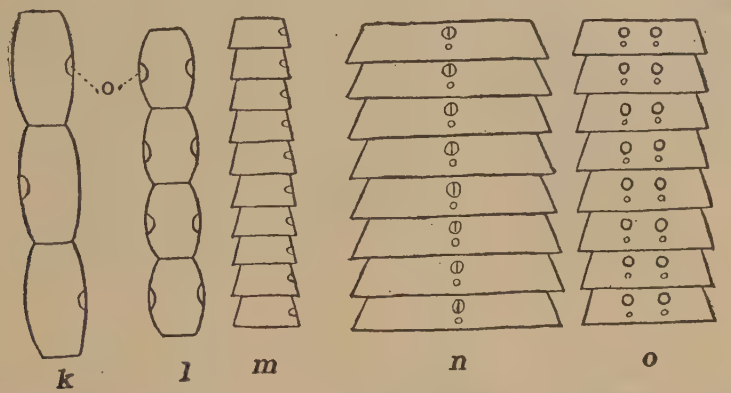


Fig. 366.—Situation of the Genital Pores in Various Cestodes: (k) Taenia; (l) Dipylidium; (m) Hymenolepis and Davainen; (n) Dibothriocephalus; (o) Diplogonoporus. Genital Orifices. In Part, After Neven-Lemaire. (From E. Brumpt, "Précis de parasitologie," published by Masson et Cie, Paris.)

the case of taenia solium), the capsule of the cysticercus is digested, and the scolex, set free, begins to grow segments.

The tapeworms of man inhabit the small intestine. They may cause no symptoms, though they often give rise to intestinal catarrh, anemia, and reflex disturbances. On examining the feces after treatment for tapeworm, the whole stool should be mixed with water and passed through a sieve; if the head of the worm be not passed, the tapeworm will grow again.

(*b*) *Varieties of Tapeworms*

In America, the fat, or beef, tapeworm (*Taenia saginata*) is the most common, though the pork tapeworm (*Taenia solium*), the dwarf tapeworm (*Hymenolepis nana*), the hydatid tapeworm (*Echinococcus*), and the broad tapeworm (*Dibothriocephalus latus*) are met with often enough to make their recognition by American physicians important. Ward's Nebraskan tapeworm (*Taenia confusa*) may prove to have a wider geographical dis-

tribution than Nebraska where, alone, it has thus far been found. In the Philippines, the Japanese double-cord tapeworm (*Diplogonoporus grandis*), and Manson's larval tapeworm (*Sparganum mansoni*) should be kept in mind.

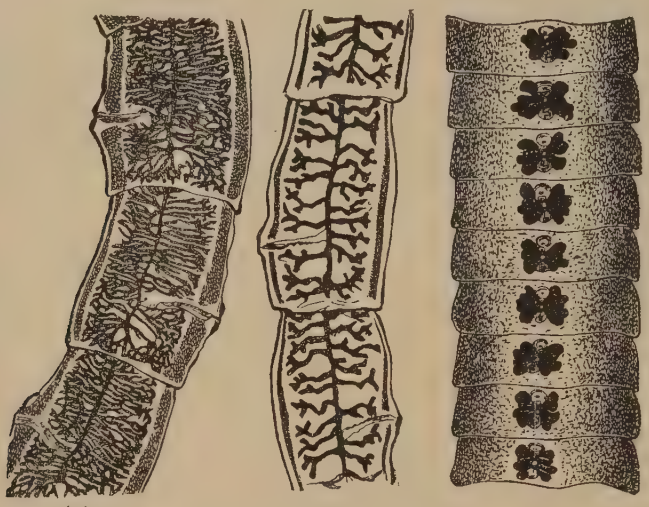


Fig. 367.—Comparison of Segments of Taenia saginata, Taenia solium, and Dibothriocephalus latus: (*a*) Segments of Taenia saginata; (*b*) Segments of Taenia solium; (*c*) Segments of Dibothriocephalus latus. (After S. F. Stein, "Die parasitären Krankheiten des Menschen," published by Moritz Schanenburg, Lahr.)

(*c*) *Human Invasions with Cestodes*

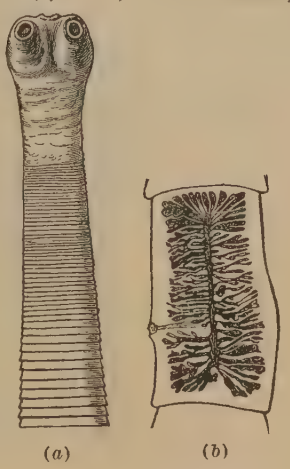
Cestode invasion in human beings is spoken of as **teniasis.** The invasion may be intestinal (*intestinal teniasis*), or somatic (*somatic teniasis*). The adult tapeworms live in the small intestine, and the diagnosis is made by finding the segments in the stools, in the bed, or in the clothes, or by finding the eggs in the feces. In somatic teniasis, the larval stages of the tapeworms may be found in the muscles, connective tissues, liver, lungs, brain, eye, or other organs (cysticercosis, echinococcosis, etc.). For the determination of a species, especially where it is at all unusual, the student should consult "The Illustrated Key to the Cestode Parasites of Man" by C. W. Stiles (Hygienic Laboratory Bulletin, No. 25, Washington, 1906).

(*d*) *The Fat Tapeworm* (*Taenia saginata*)

This is the commonest of the large tapeworms. It is less dangerous than *T. solium*, for there is no danger of auto-infection with cysticercosis.

Anemia is commoner with this species than with *T. solium*, but less common than with the broad tapeworm. It is the most difficult of all the large species to expel.

Strobila, 4-10 meters long (sometimes 1,300 segments); head, without hooks, cuboid, 1.5-2 mm. broad; 4 powerful suckers, sometimes pigmented. Genital pore, behind the middle of the lateral margin; sexually mature proglottid measures 4-6 mm. long, 8-10 mm. broad. Gravid (terminal) proglottids, 12-25 mm. long by 4-6.5 mm. broad; uterus with 15-35 slender dichotomous branches, each side of, and shorter than, the median stem. Eggs globular, one or two filaments on outer egg-shell; embryophore (or "inner shell") thick, transparent to dark brown, 30-40 μ long, 20-30 μ broad.



(*a*) (*b*)

Fig. 368.—Taenia saginata: (*a*) Head; (*b*) Ripe Segment with Uterine Contents. (After M. Braun, "Die thierischen Parasiten des Menschen," published by Bale Sons & Danielsson, London.)

The adult is known only in man. The cysticercus is found in the muscles of cattle, especially in the tongue and the masseters.

The differentiation of the egg from that of *T. solium* in the feces requires considerable experience, and physicians often confuse the two forms. The diagnosis should, therefore, not be made from the eggs, but it can be safely made by pressing a discharged segment between the two glass slides, holding the preparation to the light, and counting the lateral branches of the uterus. If the head be found, the absence of hooks distinguishes it from that of *T. solium*.

(*e*) *The Pork Measly Tapeworm* (*Taenia solium*)

Strobila 2-3.5 meters long; greatest breadth 7-8 mm.; 800-900 segments may be present. Head globular, 0.6-1 mm. in diameter (size of pin's head); 4 well developed, pigmented suckers, 0.4-0.5 mm. in diameter; armed with a rostellum, short but prominent, bearing a double row of larger and smaller chitinous hooks (22-32 in number); neck not segmented. Proglottids near the neck very short, gradually increasing in length further back. Sexually mature proglottids 2.5-3 mm. long by 4.5-5 mm. broad. Gravid (terminal) proglottids, 10-12 mm. long by 5 mm. wide; gravid uterus has 7-14 thick, lateral, dichotomous branches on each side of the median uterine stem. Genital pores irregularly alternating, slightly back of equator of segment. Eggs, oval or almost round; shell thin and usually destroyed; embryophore (often thought to be the whole egg) thick, yellowish to dark brown, 31 to 36 μ, in diameter; radial striation.

The adult worm lives in the small intestine of man; the cysticercal stage occurs in the muscles of swine ("measly pork"); occasionally, in

man, and in several other animals (monkey, bear, dog, rat, etc.). Its geographical distribution corresponds to that of the hog (cosmopolitan).

The danger of infection with **cysticercus** is greater with *T. solium* than with any other form; if a patient who harbors *T. solium* soils his

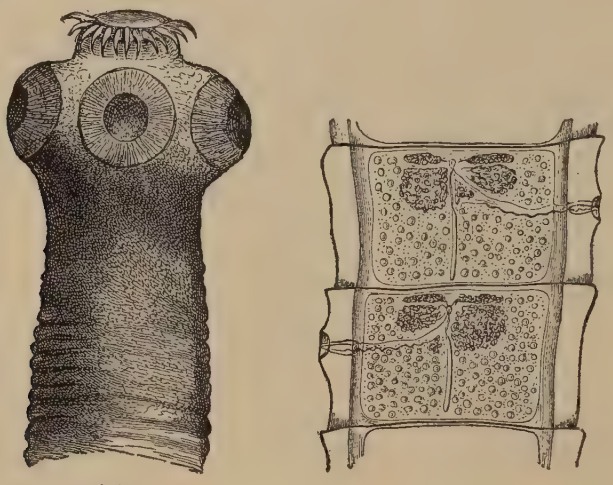


Fig. 369.—Taenia solium; (*a*) Head (*b*) Two Half-ripe Segments with Genital Organs and Vessels of Excretion. (After M. Braun, "Die thierischen Parasiten des Menschen," published by Bale Sons & Danielsson, London.)

fingers with feces containing the eggs, he may infect himself by the mouth; or a gravid segment of the worm may, by reverse peristalsis, reach the stomach where the embryos become free from their shell and bore through the intestinal wall, finally coming to rest in the muscles, eye, brain, or elsewhere, to develop into the cysticercal stage (See Cysticercosis of the Brain).

(*f*) *The Dwarf Tapeworm* (*Hymenolepis nana*)

Strobila 5-45 mm. long, 0.5-0.9 mm. at broadest part; 100-200 small segments; the smallest tapeworm known for man. Head, nearly spherical, 130 to 480 μ in

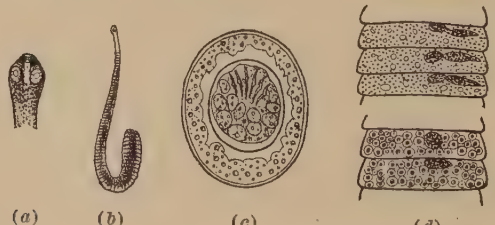


Fig. 370.—Hymenolepis nana: (*a*) Scolex; (*b*) Adult Worm; (*c*) Egg; (d) Above Unripe Below Ripe Segments. (*a, b, d,* After V. Jaksch; *c,* After Looss. In: A. Schmidt and J Strasburger, "Die Fäzes des Menschen," published by August Hirschwald, Berlin.)

diameter; well-developed rostellum, armed with single crown of 20-30 hooks. Four globular suckers. Long neck; segments near neck very short, growing longer and broader behind, but they remain broader than long except at the very end. Genital pores on left margin, near anterior border, of each segment; three testes to each segment. Gravid uterus occupies almost the whole segment; 80-180 eggs to each segment. Eggs oval, or globular, with two distinct membranes, the outer one 30-60 μ in diameter, the inner 16-34 μ, presenting, at each pole, a mammillate projection provided with filamentous appendages.

Fig. 371.—Echinoccus granulosus. In the Second Segment the Sheath for the Penis, Vagina, Uterus, Generative Glands, Shell Glands (Schalendrüse) and Vitelline Glands is Visible; on the Side Are the Testicular Vesicles. The Last Segment Shows the Uterus Filled with Eggs, as Well as the Sheath for the Penis, and the Vagina. (After M. Braun, "Die thierischen Parasiten des Menschen," published by Bale Sons & Danielsson, London.)

The adult worms live in the upper 2/3 or 3/4 of the ileum of man, and in the intestines of certain other animals (rats and mice). The embyro, when swallowed, hatches, enters a villus of the small intestine, where it becomes a cysticercus, which then falls into the lumen of the intestine and grows into an adult. In America, this tapeworm has been found in Maryland, Pennsylvania, the District of Columbia, South Carolina, Georgia and Texas.

(*g*) *The Hydatid Tapeworm* (*Echinococcus granulosus*)

Strobila, very small, this tapeworm being one of the smallest known; 2.5-5 mm., or rarely, 6.5 mm. long. Minute head, scarcely 0.3 mm. in diameter;

Fig. 372.—Scolices of Echinococcus granulosus. (After P. Krause, "Lehrb. d. klin. Diagnostik d. inner. Krankheiten," published by G Fischer, Jena.)

prominent rostellum, armed with double row of hooklets, 28-50 in number, some large, some small; suckers 0.13 mm. in diameter. Neck, and first portion of strobile, unsegmented; 3 or 4 segments. First seg-

ment about as broad as long, and sterile; second segment twice as broad and four times as long as the first; it is bisexual. The third (terminal) segment is gravid and may be 2 mm. long (over ½ the length of the worm) by 0.6 mm. broad, and contain 500 eggs.

The adult worm lives in the small intestine of carnivorous animals (dog, cat, etc.). The third or gravid segment is discharged in the feces of the dog, and the eggs gain access to the intermediate host (sheep, goats, cattle, hog, man, etc.), through contaminated food or water, or in man, possibly per os by the hands soiled by fondling an infected dog. In the stomach, the oncosphere, or 6-hooked embryo, escapes from its shell and bores its way to various organs, most often to the liver. In the larval stage it is the largest larval cestode known. It is the **echinococcus** or **hydatid cyst** of medical writers. A cyst may attain the size of a fist, or even of a child's head; it grows slowly, with thick external cuticle and thin internal layer; from the latter, broad-capsules form, in each of which several scolices develop. There may also be daughter and grand-daughter cysts.

Fig. 373.—Echinococcus Hooklets. (After Leuckart, in M. Braun's "Die thierischen Parasiten des Menschen," published by Bale Sons & Danielsson, London.)

Any organ of the human body may be affected, but echinococcus cysts occur most often in the liver, lungs, kidneys. They are more common in women than in men, and most often between the ages of 21 and 40 years. In certain localities in Europe, a peculiar form of multilocular echinococcus occurs, and it may be a different species, though this is not certain. Its nature was long misunderstood. The parasites are in the lymph vessels, but show a tendency to grow also into other channels, especially into the bile duct. The disease is usually fatal. The blood serum may yield a positive complement-fixation test with suitable antigen (Weinberg).

The fluid in echinococcus cysts is perfectly clear and contains sodium chlorid, glucose and malonic acid, but no protein. Microscopially, hooklets may be found in aspirated fluid, or heads in fluid spontaneously discharged.

(*h*) *The Broad Tapeworm* (*Dibothriocephalus latus*)

Strobila, 2-10 meters long and 20 mm. wide; color, grayish yellow to brown; 3,000-4,200 segments; each segment usually broader than long, especially in the anterior two-thirds of the strobila. Posterior segments as long as broad, or even longer. Head oblong, almond shaped, 2-3 mm. long, 0.7-1 mm. broad, with groove-like suckers. Neck thin; may be long or short. Gravid segments are 2-4 mm. long by 10-20 mm. broad. As they gradually lose their eggs, the posterior segments may be entirely devoid of eggs. The uterus is very characteristic—a "rosette spot," in the center of the segment; it has 4-6 loops on each side of the median line. Eggs brownish, elliptical, with small operculum measuring 68-71 μ by 44-45 μ. Segments break loose in chains, rather than singly.

The adult worm lives in the intestine of man, dogs, cats, and foxes. The larva is found in various fresh-water fish (pike, ling, perch, etc.). Only a few instances of infection (about 50) have been observed in the United States, though the worm is very common in some parts of Europe,

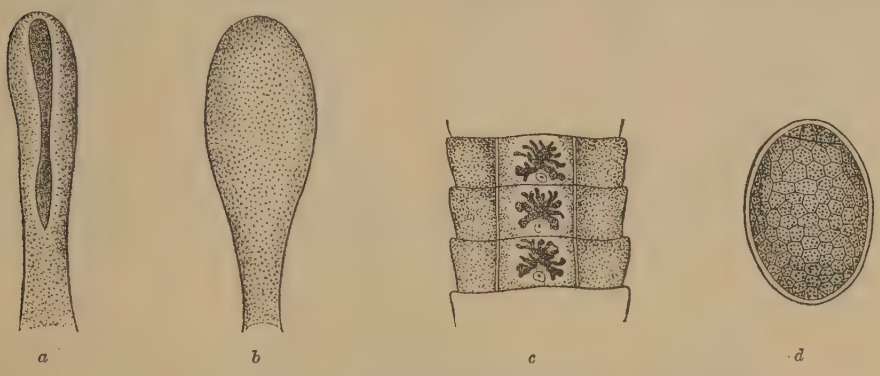


Fig. 374.—Dibothriocephalus latus: (*a*) Scolex, Surface View; (*b*) Scolex, Side View; (*c*) Ripe Segments; (*d*) Egg. (*a*, *b*, After Heller; *c*, After v. Jaksch; *d*, After Leuckart. In: A. Schmidt & J. Strasburger, "Die Fäzes des Menschen," published by August Hirschwald, Berlin.)

causing the severe dibothriocephalus anemia. In Japan, it is the most common tapeworm of man. On infection, the worm grows at the rate of 31-32 segments per day. Man contracts it by eating raw, or undercooked, fish.

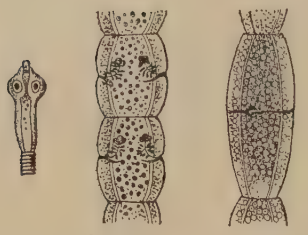
(*i*) *Ward's Nebraskan Tapeworm* (*Taenia confusa*)

Strobila 5-8 mm. in length; 8-10 mm. broad at widest part; 750-800 segments. Genital pore, back of middle of lateral region. Sexually mature segments are 4-4.5 mm. long by 3-4.5 mm. broad. Gravid (terminal) segments are 27-35 mm. long by 3.5-5 mm. broad. Length of segments exceeds breadth in nearly entire worm. Uterus has 14-18 thick, short, dichotomous branches on each side of median stem. Eggs oval, 39 by 30 μ.

The adult worm lives in the intestine of man. The cysticercus is unknown. The worm has been found in Lincoln, Nebraska, but probably has a wider distribution.

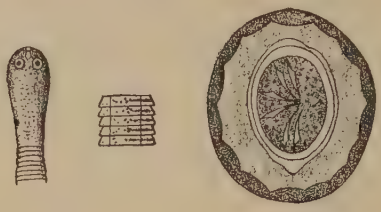
(*j*) *Other Tapeworms*

Man in rare instances is an accidental host for the double-pored tapeworm of dogs and cats known as *Dipylidium caninum.* Rarely, also, invasion with the flavopunctate tapeworm of rats, known as *Hymenolepis diminuta,* is met with. For other rare forms of tapeworm the articles of Stiles should be consulted.



a *b* *c* *d*

Fig. 375.—Dipylidium caninum: (*a*) Scolex; (*b*) Unripe Segments; (*c*) Ripe Segment; (*d*) Egg. (*a, d,* After Diamare; *b, c,* After v. Jaksch; A. Schmidt & J. Strasburger, "Die Fäzes des Menschen," published by August Hirschwald, Berlin.)



a *b* *c*

Fig. 376.—Hymenolepis diminuta: (*a*) Scolex; (*b*) Segments; (*c*) Egg. (*a,* After Zschokke; *b, c,* After Grassi; A. Schmidt & J. Strasburger, "Die Fäzes des Menschen," published by August Hirschwald, Berlin.)

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4. The Flukeworms (Trematodes)

(*a*) *General Characters*

The *Trematodes* are one of the five orders of *plathelminthes.* It is a parasitic order. The body is naked in the adult state and not segmented. It is provided with an incomplete digestive tube without anus, and it has an oral, or an oral and a ventral sucker. The life cycle is complicated and may involve two or more generations that live outside of man. In some instances an intermediate host is required, but in others direct infection may occur.

(*b*) *Human Invasion with Trematodes*

All the trematodes that interest us medically belong to the suborder of distoma, which is divided into several families. The genera that in-

fect human beings are (1) *Fasciola*, (2) *Clonorchis*, (3) *Opisthorchis*, and (4) *Schistosomum*. The trematodes may invade different organs of human beings. The condition is known as *distomatosis* or *distomiasis* (pulmonary, hepatic, intestinal, venal, ophthalmic, etc.). Except the blood flukes, the parasites are all hermaphrodites.

For American physicians, these parasites are of but little importance at present, as only a few cases have been met with in this country, and

Fig. 377.—Trematodes. (After P. Krause, "Lehrb. d. klin. Diagnostik d. inner. Krankheiten," published by G. Fischer, Jena.)

they, with the exception perhaps of the liver fluke and the blood fluke, have all been imported cases.

In Asia, the lung fluke (*Paragonimus westermanii*) is an important

parasite, causing *parasitic hemoptysis* (pulmonary distomatosis). When I was in Tokyo, Dr. K. Miura showed me a patient suffering from this disease, and demonstrated the eggs in the unstained sputum. The egg is yellow, 77 to 102 by 40 to 75 microns, with distinct operculum, but containing no miracidium when discharged.

The common European liver fluke (*Fasciola hepatica*), the Asiatic liver fluke (*Opisthorchis sinensis*), the African blood fluke (*Schistosoma hematobium*), the Asiatic blood fluke (*Schistosoma japonicum*), are all important medically. Though true intestinal distomatosis is rare (being occasionally due to *Fasciolopsis buskii, Fasciolopsis rathouisi,* etc.), the eggs of the liver flukes, which cause hepatic distomiasis, and the eggs of the blood flukes, which cause venal distomatosis or billharziosis, are sometimes found in feces, and will, therefore, be described here, along with the parasites that deposit them.

(*c*) *The Liver Flukes*

No less than six different species of liver flukes, representing three different genera (*Clonorchis, Opisthorchis,* and *Fasciola*), are known in connection with hepatic distomatosis. Of these, by far the most important is the Asiatic liver fluke.

i. The Asiatic or Japanese Liver Fluke (Clonorchis sinensis)

Parasite, an elongate, lanceolate, non-spinose trematode. Testes located caudally, characteristically branched. Eggs dark brown, with sharply defined operculum, occasionally with small knob at posterior end; ciliated miracidium present at oviposition.

The infection occurs from eating raw fish. In certain Japanese districts 20 per cent of the population is infected; in three villages studied by Katsurada, over 60 per cent was infected. There may be from 2,000 to 5,000 of the parasites in a single human cadaver.

The diagnosis is made by finding the egg in unstained feces. Clonorchiasis may be suspected in infected districts by the occurrence of enlargement of the liver with bloody diarrhea.

ii. The Siberian Liver Fluke or European Cat Fluke (Opisthorchis felineus)

Parasite, a lanceolate, non-spinose trematode; 8-15 mm. long, by 1.25 to 2.5 mm. broad. Testes lobate, not branched. Eggs, oval, yellow brown, 26 to 30 x 11 to 15 microns, one side flatter than the other; operculum, sharply defined (on acuter pole), contains a ciliated miracidium at oviposition. The adult worms live in the bile ducts; they are occasionally found in the duodenum and in the pancreatic ducts.

The embryos hatch in snails. Man is infected by eating raw fish. European cats are often infected.

The diagnosis of Siberian opisthorchiasis is made in the same way as for the Asiatic liver fluke.

In India, a similar liver fluke (*Opisthorchis noverca*) has been observed, but thus far only two instances of Indian opisthorchiasis have been reported.

In the United States, it was thought that the European cat-fluke had been found, but it turned out to be a different one (*Opisthorchis pseudofelineus*).

iii. The Common Liver Fluke (Fasciola hepatica)

The parasite is a flat, leaflike, spinose worm, 18-30 mm. long by 13 mm. broad; intestine, testicles, ovary and vitellogene glands, profusely branched. Eggs oval, yellow brown, 130-145 by 70-90 microns, with distinct operculum, not containing a miracidium when oviposited. Snails of the genus *Limnaea* form the intermediate host; infection occurs by swallowing encysted cercaria (on plants in marshes).

Hepatic fascioliasis seems to be accidental and not very common in man, the normal hosts being cattle, goats and sheep.

The eating of raw infected liver of goats causes a disease known as *halzoun* in Syria. The parasites attach themselves to the pharyngeal mucosa, like leeches. The toxins cause local vasodilatation and other severe symptoms (dyspnea, aphonia, itching in the throat, etc.). The disease is often fatal.

(*d*) *The Blood Flukes*

There are two principal varieties—the African and the Asiatic.

i. The African Blood Fluke (Schistosoma hematobium)

This is the more common. It is found chiefly in Africa, but occurs also in Persia, Arabia and India, and in Panama, Cuba and Porto Rico.

Male, 4-15 mm. long by 1 mm. broad; sides curved ventrally to form the gynecophoric canal; worm armed with spinose warts. Female, filiform, 15-20 mm. long; lives in the gynecophoric canal of the male. Eggs oval, 135-160 x 55-66 microns; provided with a spine but not with an opereulum.

ii. The Asiatic Blood Fluke (Schistosoma japonicum)

This parasite, recently discovered, is found in Japan, China, the Philippines and South Africa.

The males are narrower, and the females shorter, than those of the African species. The eggs, also, are smaller, and have neither spine nor operculum, though, near one pole, they show a small knob.

Infection with these two forms of blood fluke probably takes place through the skin. The young worms live in the veins of the liver, and in the veins of the intestine and bladder wall. The eggs are deposited in various organs while the parasites wander from the portal vein to the

pelvis. The ova increase in size as they work through the tissues into the lumen of the intestine or of the bladder; they sometimes develop into a ciliated embryo (miracidium), which may be visible in the egg when it is voided in the urine. *It is the eggs, rather than the worms, that do harm,* especially in rectal, renal and vesical bilharziosis. Hematuria is the most important symptom; the **endemic hematuria** of Egypt is due to *S. hematobium.*

The *diagnosis* is made by microscopic examination of the urine and feces for eggs of the parasites. They are most common in the last few drops forced out at the end of micturition, and in scrapings from polypoid growths in the rectum. Venal distomiasis, or Bilharziosis, must be differentiated (1) from filarial chyluria, (2) from vesical calculus, (3) from gonorrhea, (4) from hemorrhoids, and (5) from neoplasms.

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5. The Round Worms (Nemathelminthes)

(*a*) *Classification of the Nemathelminthes*

The *Nemathelminthes* include three orders, (1) *Nematoda,* (2) *Gordiacea,* and (3) *Acanthocephali.*

The *nematodes* are cylindrical worms, usually slender, and provided with a complete digestive tube. The surface of the body shows sometimes irregular rings that do not correspond to any internal segmentation. The sexes of the nematodes that invade human beings are separate. The nematodes include (1) *Ascaris,* (2) *Oxyuris,* (3) *Anchylostomum,* (4) *Necator,* (5) *Trichocephalus,* (6) *Trichinella,* (7) *Filaria,* and (8) *Strongyloides.* There are a number of other genera that are parasitic for man, but they are so rare that they may be omitted here.

The worms (except Filaria and Trichinella) develop directly, without intermediate stages. There is a mouth at one end, while the intestine opens usually on the abdominal surface, rarely behind. The females are larger than the males; the vulva lies in the middle of the abdomen. In the males, the generative organs open close to the posterior extremity into

the terminal portion of the alimentary canal; the tail-end is often rolled up. The eggs are enclosed in a chitinous or calcified hull, which is transparent, but very resistant.

The *Acanthocephali*, or thorny round worms, include *Gigantorhynchus*, while the *Gordiacea* include several parasites only rarely present accidentally in man.

(*b*) *The Parasitic Nematodes*

i. The Eelworm (Ascaris lumbricoides)

The worms are cylindrical, but taper off to a point at both extremities, like earth worms. Color, grayish to reddish yellow. The head has three conical lips. Males, as long as 25 cm. (thickness 3 mm.); females, reach a length of 20-40 cm. (thickness 5 mm.), and are oviparous. Eggs, nearly round; in the feces, yellowish

Fig. 378.—Ascaris lumbricoides: (*a*) Female; (*b*) Egg; (*c*) Male and Female. (After P. Krause, "Lehrb. d. klin. Diagnostik d. inner. Krankheiten," published by G. Fischer, Jena.)

brown, measuring 50-75 by 36-55 microns; they are unsegmented when oviposited, and have a thick, mammillate covering.

The adult worms live in the upper portion of the small intestine of man; usually, only one or two are present; occasionally, large numbers. The development is direct, without intermediate host. The eggs, in discharged feces, slowly develop to embryos, which, swallowed in contaminated drinking water or fruits, develop into adult worms.

The worms may crawl into the stomach, or even into the throat, occasionally passing into the trachea and lung. Rarely, they pass through

the eustachian tube. Sometimes they enter the bile ducts and may cause abscess of the liver. Were it not for the wanderings of these erratic ascarids, ascariasis would scarcely be feared, since, ordinarily, the invasion is innocuous.

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ii. The Pinworm (Oxyuris vermicularis)

Males 4 mm. long, with blunt tail-end, bearing six pairs of papillae. Female, 10 mm. long; tail-end sharp. The head presents three small nodular lips. Eggs, somewhat asymmetrical, oval, 50-52 microns long; 16-24 microns broad; contents granular, or the embryo itself may be visible.

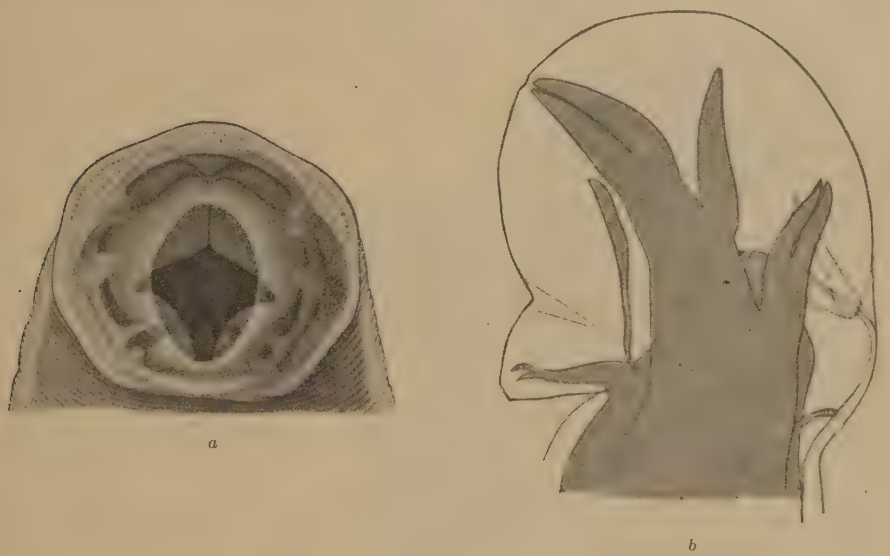
Fig. 379.—Oxyuris vermicularis: (*a*) Egg with Embryo; (*b*) Female. (After P. Krause, "Lehrb. d. klin. Diagnostik d. inner. Krankheiten," published by G. Fischer, Jena.)

In the early stages of development, the parasites live in the small gut, where they copulate. The males soon die. The females wander to the cecum and later to the colon. Pinworms tend to wander out of the anus; they cause characteristic anal itching, especially at night, when the worms migrate. On scratching to relieve the irritation, eggs get under the fingernails, and recurring auto-infection (by nose or mouth) is explained. Oxyuriasis is most common in children of from 3-10 years, but it may occur at any age.

iii. The Hookworms (Necator and Ankylostomum)

At least two varieties of hookworm are parasitic in man. The Old World hookworm, which is the cause of Egyptian chlorosis, miner's anemia, etc., is the *Ankylostoma duodenale.* The New World hookworm, which causes the hookworm anemias of the Southern United States and of Porto Rico, and of the miners of Pennsylvania, is the *Necator americanus.*

The New World Hookworm (Necator americanus (Stiles, 1902), or Uncinaria americana (Stiles, 1902).—This round worm is 7-11 mm. long, and has a dorsal and a ventral pair of lips at the mouth, a prominent dorsomedian buccal tooth, and four buccal lancets. In the female, the vulva is in the oral half of the body; in the male, the dorsal ray of the bursa is divided at the base, and there are two tips to each branch. Eggs,



a *b*

Fig. 380.—Necator americanus: (*a*) Mouth Parts; (*b*) Caudal Bursa. (After A. Looss, "Anatomy and Life History of Agchylostoma duodenale," published by the School of Med., Cairo.)

thin-shelled, 64-72 microns long by 36-40 microns broad; oval, with rather blunt poles.

The Old World Hookworm (Anchylostoma duodenale (Dubini, 1843).—Worm, 8-18 mm. long; in its mouth, (a) two pairs of strong, curved, ventral teeth, (b) one pair of knoblike dorsal teeth, the dorsomedian tooth being nil or practically so, and (c) a pair of ventral lancets. In the male, the dorsal ray of the bursa is divided for 2/3 its length from the base, and there are three tips to each branch. In the female, the vulva is in the caudal half of the body. Eggs 52-61 microns long by 32-38 microns broad; oval; very bluntly rounded ends.

Uncinariasis and Ankylostomiasis in Human Beings.—The adult worms live in the small intestine, especially in the jejunum and the ileum, but they also occur in the duodenum, and, sometimes, in the stomach.

The eggs of hookworms oviposited in the intestine and escaping with the feces begin to develop outside; in about twenty-four hours, rhabditiform embryos have been formed, which shed the skin (ecdysis) after some 48-72 hours; a second shedding occurs in 5-9 days, when the worm

reaches the infecting stage, or so-called "encysted larva"; it now takes no more food until it reaches man. Human beings may be infected in either one of two ways; (1) the larvae may pass through the skin (especially of bare feet) and reach the blood; passing through the heart to the lungs, they go through the air passages to the larynx, down the gullet to the stomach and thence to the small intestine; (2) the larvae may be

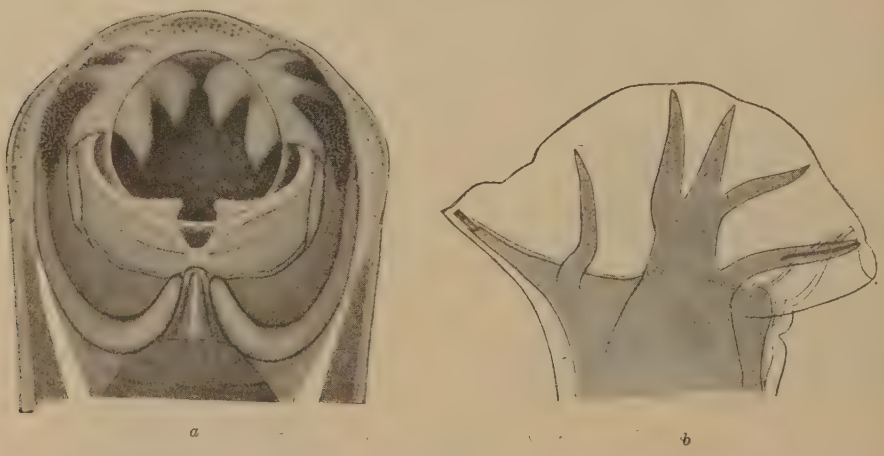


Fig. 381.—Ankylostoma duodenale (agchylostoma): (*a*) Mouth Parts; (*b*) Caudal Bursa. (After A. Looss, "Anatomy and Life History of Agchylostoma duodenale," published by the School of Med., Cairo.)

taken into the mouth with food or water, or from hands soiled by earth containing the larvae. The doctrine of skin infection (Looss) is now generally adopted as the most common mode of access to the body. Uncinariasis, or hookworm disease (*q. v.*) is one of the most important of the diseases met with by American physicians, but it is often overlooked.

Stiles has shown the enormous prevalence of the disease in the Southern States, and Ashford, King and Guterriez state (1911) that in Porto Rico over 300,000 people, or nearly one-third of the total population of the Island, have now received specific treatment for uncinariasis.

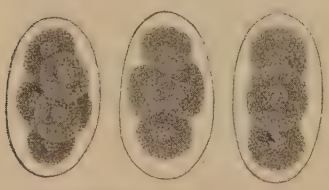


Fig. 382.—Eggs of Necator americanus. (After A. Looss, "Anatomy and Life History of Agchylostoma duodenale," published by the School of Med., Cairo.)

The principal harm done by the worm appears to be due to the production of a toxin, though the actual loss of blood due to the worms is a factor also to be considered.

Eggs in Feces.—The diagnosis is made by finding the eggs in the feces microscopically (there may be as many as four million eggs in a single stool!), or by finding the adult worms after the administration of thymol.

The eggs, which appear in the feces in from six to ten weeks after infection, are usually discoverable by ordinary examination of a particle of feces diluted on a glass slide (at least 10 slides should be examined before rendering a negative report); but when they are not numerous in the feces, they may be concentrated by the method of Pepper, or that of Bass.

Pepper's Method.—This is based upon the fact that hookworm ova tend to stick to the glass slide. If some diluted feces, prepared for microscopic examination on a glass slide, be permitted to settle, and the slide be then immersed in water, most of the fecal matter will be removed, while the ova stick to the slide.

Bass's Method.—This is based upon centrifugalization. The feces are first diluted with ten, or more, times their volume of water; then centrifuged, and the supernatant fluid, containing vegetable débris, poured off. Upon the sediment, which contains the hookworm eggs, is poured a calcium chlorid solution (specific gravity 1.050). The tube is again centrifuged and decanted. Then a calcium chlorid solution of a specific gravity of 1.250 is added, and the mixture again centrifuged. The hookworm eggs will now be on the surface, and may be pipetted off. Often, a mass of almost pure hookworm eggs is thus obtained.

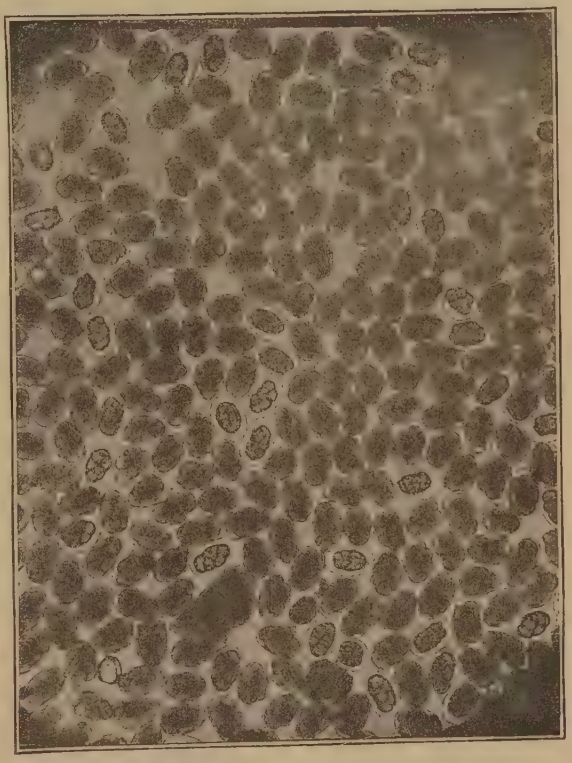


Fig. 383.—Preparation of Hookworm Ova Made from Feces by Bass's Method. They Appear About As Large As They Do With a 1-6 Objective and a 2-inch Eyepiece. (G. Dock and C. C. Bass, in "Hookworm Disease," published by C. V. Mosby Co., St. Louis.)

Blotting-paper Test.—In pioneer districts, where physicians and microscopes are not available, the blotting-paper test of Stiles may be used, in making a probability diagnosis. An ounce, or more, of feces are folded in white blotting paper, or even in white newspaper, and allowed to stand for several hours; the paper is then unwrapped and examined for a blood stain. Of course this crude method will be resorted to only when a better test cannot be made.

The Adult Worms in Stools.—After an anthelmintic (thymol, or Baltimore oil), the worms may be found in the stools. The anterior end is curved dorsally to form a "hook." The stools should be placed in a pail, stirred with several volumes of water, and the supernatant fluid poured off, the process being repeated several times. The sediment is then placed on a glass plate, over a black background, and the small, whitish, grayish, or reddish

brown worms looked for. If found, the finer points can be studied under the microscope.

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iv. The Whipworm (Trichuris trichiura)

Formerly known as *Trichocephalus dispar.* The worm lives in the colon, especially in the cecum. It is probably the commonest intestinal worm in America. As a rule, trichocephaliasis causes no symptoms, and is an unimportant invasion.

Anterior part slender, posterior part shorter and thicker, so that the worm resembles a whip. Males, 40-50 mm. long; females, a little longer. Eggs, numerous; characteristic; brown, large, with thick shell and unsegmented protoplasm; a light spot, resembling an aperture, is visible at each pole.

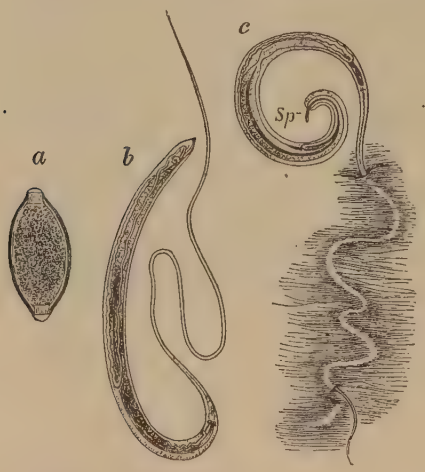

Fig. 384.—Trichuris trichiura: (*a*) Egg; (*b*) Female; (*c*) Male, with the Fore-end Buried in Intestinal Mucosa. (After Claus, in M. Braun's "Die thierischen Parasiten des Menschen," published by Bale Sons & Danielsson, London.)

v. The Worm of Trichinosis or Trichiniasis (Trichinella spiralis)

There are *three stages* of the parasite: (*a*) the adults, (*b*) the embyros, and (*c*) the encysted larvae.

(*a*) The **adult worms** live in the duodenum and jejunum of man, the hog, the rat, and various other animals (dog, cat). Males, 1.4-1.6 mm. long

by 40 microns in diameter. Females, 3-4 mm. long by 60 microns thick. Circular on cross section. Esophagus supported by a single row of cells known as the cell-body; males, without spicules, die shortly after copulation; females, viviparous, the site of the vulva about 1/5 the length of the body from the mouth; remain in lumen of intestine, or in lymph spaces, for several weeks, depositing their young (200-1,500 or more per female), not in the lumen of the intestine, but in the lymph channels of the villi.

(*b*) **Embryos** are 90-100 microns by 6 microns broad. They wander through the lymph channels into the blood, and thence, by way of the arteries, or, even directly through the tissues, to the voluntary muscles, reaching these in about ten days after the infection. They pass through the sarcolemma, entering the muscle fibers, where they develop, in the fourth or fifth week, into rolled-up spirals. By the second or third month, these become

Fig. 385.—Trichinella spiralis: (*a*) Female; (*b*) Male; (*c*) Encysted. (After P. Krause, "Lehrb. d. klin. Diagnostik d. inner. Krankheiten," published by G. Fischer, Jena.)

(*c*) **Encysted larvae**, measuring 400 by 250 microns. The capsule, at first fibrous, may later become calcified. Such larvae may live there for years (thirty or more) and represent the infecting stage ("fleshworm") found in the hog. The heart muscle escapes. The most active voluntary muscles (*e. g.*, intercostals, diaphragm, tongue, and laryngeal) are predominantly involved. It is estimated that as many as 100 millions may be present in a single person. If swallowed, in raw, or imperfectly cooked, pork or sausage, the cyst is digested in the stomach, and the larvae pass into the small intestine, developing in a couple of days to the adult stage. The females become impregnated, and contain embryos in the uterus within a week after the infected meat is swallowed.

The infection in man is known as *trichinosis*, or *trichiniasis* (*q. v.*).

The *diagnosis* may be suspected in typhoidlike epidemics after German picnics, or parties at which pork, or sausage, has been served. Any pork left should be examined.

The *adult worms* may be sought for in the stools (small, hairlike objects), but this method rarely helps in diagnosis, as the worms are seldom found.

The patient's *blood* should be studied for leukocytosis and eosinophilia (T. R. Brown), which may reach 30 or more per cent; if there be doubt, by the third week, or later, a minute piece of the deltoid muscle may be excised and examined for larvae. In some cases, the embryos

are demonstrable in the blood of the patient. One draws 20-50-100 c.c. from a vein, mixes with 1 per cent to 3 per cent acetic acid to decolorize the red corpuscles, centrifugalizes, and stains the sediment with eosinate of methylene blue. A method of diagnosis by *complement-fixation* has been worked out (Stroebel). In this, the serum of the patient under suspicion is mixed with an alcoholic antigen extract obtained from muscle-trichinae isolated by pepsin digestion of the muscles; in positive cases the hemolysis in a hemolytic system is inhibited. The test may be positive for $1\frac{1}{2}$ years after invasion.

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vi. The Cochin-China Worm (Strongyloides stercoralis)

This worm is common in tropical and subtropical regions. It is especially common in China, India and Japan. Strongyloidosis occasionally occurs in America; we see it now and then in the Baltimore clinics (Thayer). It is very common in Porto Rico. Strong has found the worm in monkeys, as well as in man.

I. (*a*) The *parasitic adults,* living in the human intestine, are parthenogenetic females, 2.2-3 mm. long by 34-70 microns broad; esophagus ¼ as long as body; double uterus present, with 3 to 6 segmenting eggs in each horn. The eggs measure 50-59 by 30-34 microns; they escape through the vulva (in the posterior third of the body of the worm) to be deposited in the intestinal lumen of the host, or in galleries made by the females in the mucous membrane. These eggs develop into:

(*b*) *The rhabditiform embryos,* 200-240 microns long by 12 microns broad. They may grow to be 600 μ long by 20 μ broad by the time the feces are discharged. In two or three days, these embryos develop in the feces outside into

II. (*c*) *Free-living dioecious adults* (*i. e.,* the males and females are separate creatures). Males, 0.7 mm. long, with a tail curved ventrally to form a hook. Females, 1 mm. long, vulva a little behind equator of body; each female develops 30-40 eggs, which develop to form

(*d*) *Free-living rhabditiform embryos,* 220 microns long; they grow to a length of 550 microns, when they moult and change into

(*e*) *Filariform larvae,* with elongated cylindrical esophagus, half as long as

the body. These embryos—the infecting stage—enter man, either by the mouth in drinking water, or through the skin; they reach the duodenum and upper jejunum, and there develop directly into (*a*) the parthenogenetic females.

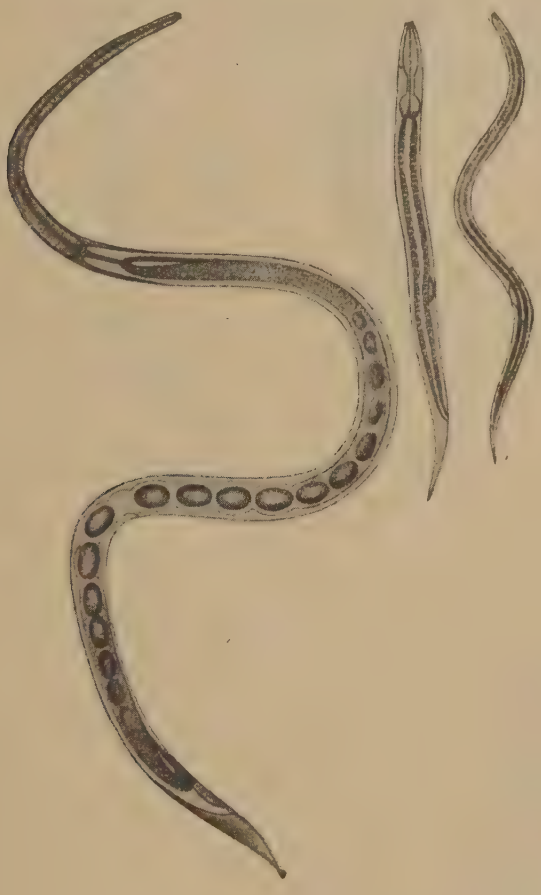

Fig. 386.—Strongyloides stercoralis. On the Left is a Gravid Female From the Intestine of Man. In the Middle is a Rhabditiform Embryo from a Fresh Preparation of Feces. On the Right is a Filariform Embryo from a Culture. (After M. Braun, "Die thierischen Parasiten des Menschen," published by Bale Sons & Danielsson, London.)

This complete life cycle (*a-b-c-d-e-a*) is an alternation of a dioecious with a parthenogenetic generation (alloiogenesis); in the temperate zone, an abridged cycle (*a-b-e-a*) may occur.

The *diagnosis* is made by finding the rhabditiform embryo (*b*) in the fresh feces. Occasionally, after purging, the eggs, strung together end

to end, and surrounded by a delicate tube, may be found in the stools. The disease in human beings is spoken of as *strongyloidosis.*

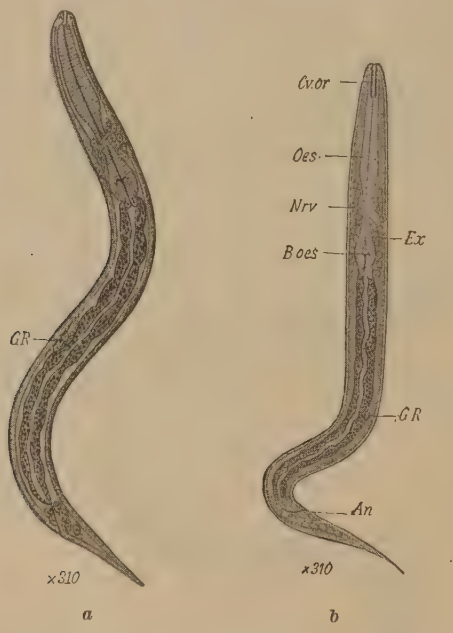

Fig. 387.—Comparison of larvae: (*a*) Strongyloides stercoralis; (*b*) Ankylostoma duodenale. (After A. Looss, "Anatomy and Life History of Agchylostoma duodenale," published by the School of Med., Cairo.)

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vii. Toxocara canis

This worm, not uncommon, may be met with as an accidental finding in man.

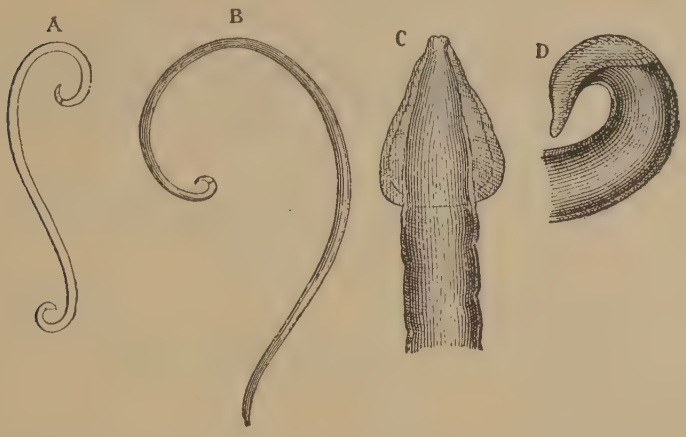

Fig. 388.—Toxocara canis: (A) Male; (B) Female; (C) Anterior Extremity Enlarged and Shown from Dorsum to Exhibit the Lateral Winglike Cuticular Expansions; (D) Same Shown in Profile. (Tyson, after Railliet, in R. W. Webster's "Diagnostic Meth.," published by P. Blakiston's Son & Co., Phila.)

6. Larvae of Parasitic Insects in the Feces

Various dipterous larvae, the "grub" stage of insects, have been reported as chance parasites in the intestine (*intestinal myiasis*). These are usually swallowed accidentally with food or water. The "grubs," or "bots," are easily recognized in the feces. They are of but little medical significance.

The larva of the fly *Compsomyia macellaria* is known as the "screw worm." This fly oviposits in wounds, and in the nostrils (especially of ozænous patients) who sleep in the open air. The eggs develop into larvae within a few hours, and these larvae burrow in the tissues. A fatal result is not uncommon.

The occurrence in the feces of the common cheese-mite (*Tyroglyphus siro*) and of its ova has been emphasized by R. S. Morris.

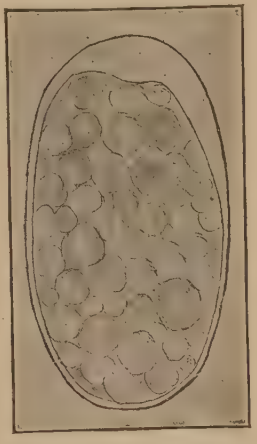

Fig. 389.—Egg of Tyroglyphus siro. (After R. S. Morris.)

When any unusual parasite or ovum is found in the feces, and on examination it is not easy to identify it, it should be preserved in 50-70 per cent alcohol, or in 2 per cent formalin solution, and sent to the Hygienic Laboratory, U. S. Public Health Service, Washington, D. C., for identification.

H. Special Examination of the Pancreas and Its Functions

1. Physiology of the Pancreas

The *functions* of the pancreas are divisible into two parts, (1) those of the external secretion (pancreatic juice), and (2) those of the internal secretion.

As regards the *external secretion,* the constituents of the pancreatic juice and the relation of its ferments to the digestion of protein, fats, and starch, have already been referred to.

As to the function of *internal secretion,* its great importance for the intermediary metabolism of carbohydrates is now generally recognized.

The pancreas lies so deep in the abdomen that it is almost inaccessible to physical examination, except in special cases. In the diagnosis of pancreatic diseases, therefore, we have to rely chiefly upon functional diagnosis. Methods in the latter direction have advanced so rapidly in recent years that many cases of pancreatic disease can now be detected early.

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2. Epitome of Symptoms and Signs Suggestive of Pancreatic Disease

For convenience, these may be tabulated as follows:

Signs of Pancreatic Insufficiency.—When both the external secretion and the internal secretion are extensively involved, protein and fat can be only partially utilized during digestion, and the carbohydrates absorbed go out as glucose in the urine (glycosuria). The result is rapid emaciation and cachexia.

If the external secretion, alone, be involved, the assimilation of proteins and fats is interfered with, and muscle fibers and free fat appear in the stools. The **stools** are bulky, and contain much undigested protein (*azotorrhea*) and much neutral fat and fatty acid crystals, giving the stools in the severer cases a "buttery" appearance (*steatorrhea*). When the interference with the external secretion is only partial, the azotorrhea and steatorrhea may not be recognizable macroscopically or microscopically, but must be determined by quantitative chemical studies of the feces, or by Sahli's glutoid test, or Schmidt's meat-bag nucleus test, or the duodenal contents obtained after an oil-meal or by Einhorn's duodenal pump may be examined for pancreatic constituents.

Sometimes, the internal secretion is involved simultaneously with the external secretion, in which event glycosuria accompanies pancreatic stools; in other cases, the internal secretion may be involved without simultaneous involvement of the external secretion. In such cases, there may be diabetes mellitus, or alimentary glycosuria; but it may be impossible, clinically, to be sure that these conditions are pancreatic in origin.

Pancreatic Pain.—Violent, deep-seated, epigastric pain (so-called "stablike, celiacus pain"), associated with vomiting and collapse, accompany acute hemorrhagic pancreatitis. The pain in pancreatic colic, due to stones in the duct of Wirsung, may closely resemble that of biliary colic, but it is not accompanied by jaundice. The epigastric pain in pancreatic cysts, and in carcinoma of the pancreas, may radiate to the back, shoulders, or sternum; occasionally, if the head of the pancreas be involved, it may radiate to the right hypochondrium.

Mass in the Pancreatic Region.—This may be due to gangrene, abscess, cyst, or cancer of the pancreas. In gangrene and abscess, the symptoms are acute, and there is fever and leukocytosis. In cyst, the tumor is situated between the ensiform and the navel, is spherical, smooth, and

usually fluctuates. In cancer, a tumor-mass is palpable in only about one-quarter of the cases.

Stones Arising in the Pancreatic Ducts.—These may be found in the feces. They should be recognizable in the ducts by x-ray examination, since they usually consist of lime salts.

Hemochromatosis.—This peculiar pigmentation of the skin is recognizable by the naked eye and on microscopic examination of bits of excised skin. The cutaneous pigmentation is usually associated with deposits of pigment in the interstitial tissue of the liver and of the pancreas. When the pancreas is much involved, glycosuria occurs (bronzed diabetes).

Lipasuria.—If fat necrosis be suspected, lipase may be demonstrable in the urine, and, if found, supports the suspicion.

Signs of Pressure on Organs Near the Pancreas.—In cicatricial processes and neoplastic processes in the pancreas, there are often signs of pressure upon adjacent organs, including (a) the *bile duct* (causing jaundice and distension of the gall-bladder), (b) the *portal vein* (causing ascites and hemorrhoids), (c) the *inferior vena cava* (causing edema of the lower extremities), (d) the *gastro-intestinal tract* (causing gastro-duodenal or colonic symptoms), (e) the *left ureter* (causing hydronephrosis), (f) the *superior mesenteric vessels.* A jaundice that does not recede, and which is accompanied by a palpable dilatation of the gall-bladder, is highly suggestive of cancer of the head of the pancreas, or of chronic (cirrhotic) pancreatitis, since jaundice due to gall-stones is usually associated with contraction of the gall-bladder.

Other Points to be Considered.—The etiological factors present in the case should always be considered in making a diagnosis of pancreatic disease. A history of epigastric trauma or of preceding gall-stone attacks may be important. Arteriosclerosis stands in definite relation to some forms of pancreatic atrophy and cirrhosis with diabetes. Most pancreatic diseases occur after middle life (40-60).

3. Physical Examination of the Pancreas; Determination of Its Form, Size and Position

(*a*) *Anatomical Relations*

The pancreas lies deep in the abdominal cavity in the umbilical region. The head (*caput pancreatis*) lies at the level of the second and third lumbar vertebrae, surrounded by the concavity of the duodenum; the body (*corpus pancreatis*) lies transversely, in front of the aorta and inferior vena cava, at the level of the first and second lumbar vertebrae; the tail (*cauda pancreatis*) extends into the left hypochondrium, coming into contact with the anterior surface of the left kidney and the medial surface of the spleen.

The area on the anterior abdominal wall, corresponding to the portion of the ductus choledochus related to the head of the pancreas, can be found as follows:

Draw a perpendicular and a horizontal line through the navel; next, divide the right upper quadrant by a line that bisects the apex of the right angle at the navel. The *regio pancreatico-choledochica* lies between the vertical line and this line, not extending more than 5 cm. along this line, and below not reaching as far as the navel. This localization is fairly exact, except in obese people, in whom the navel tends to be displaced downward.

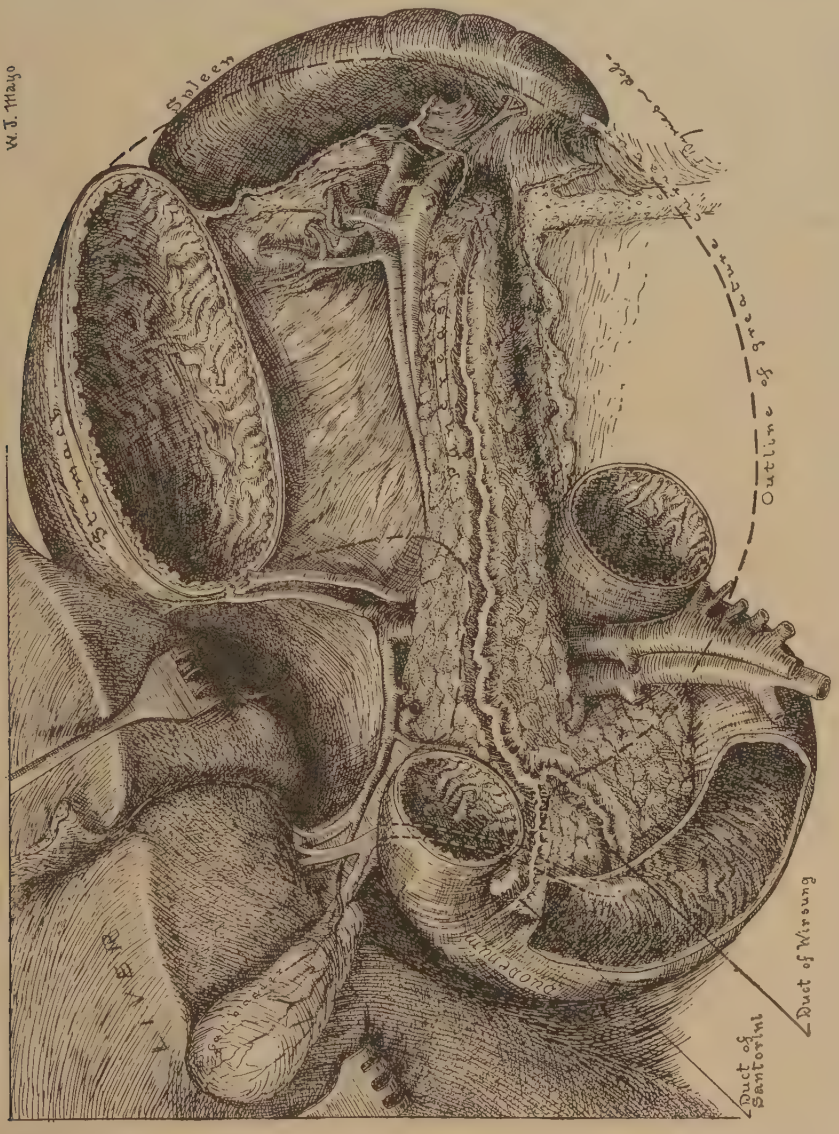

Fig. 390.—Diagram Showing Relation of Pancreas to Stomach, Duodenum and Liver. (After W. J. Mayo, Collected Papers by the Staff of St. Mary's Hospital, Mayo Clinic, published by W. B. Saunders Co., Phila.)

(*b*) *Inspection of the Pancreatic Region*

In the pancreatic region, there may be a visible swelling, due to disease of the pancreas (abscess, gangrene, cyst, tumor), but in the major-

ity of pancreatic diseases, inspection reveals nothing. Hemochromatosis of the skin should be kept in mind.

(*c*) *Palpation of the Pancreas*

The organ is rarely accessible, except in pathological cases accompanied by large inflammatory exudate, neoplastic growth, or cyst formation. Occasionally, in emaciated patients, when the stomach and intestine are empty, it may be possible to palpate the pancreas. Visceroptosis with relaxation of the abdominal walls makes palpation easier. The head of the pancreas can sometimes be felt as a firm, movable mass between the right sternal and the right parasternal line in the regio pancreatico-choledochica above described. When there is marked diastasis of the recti muscles, the palpating hand can sometimes be introduced between the muscles, shoving the skin in front of it into the abdominal cavity, and the pancreas palpated throughout its whole extent.

With the exception of cysts, all tumors of the pancreas lie behind the gastro-intestinal tube. **Pancreatic cysts** may present in any one of three situations: (1) between the stomach and the colon; (2) above the lesser curvature of the stomach; and (3) between the layers of the mesocolon. Most pancreatic tumors, since they lie behind the intestine, tend to become separated from the palpating hand during inspiration. Some cysts possess mobility (manual, respiratory).

If a *carcinoma* of the head of the pancreas be palpable, it is usually nodular, hard and tender. In *chronic indurative pancreatitis,* the firm head of the pancreas is often erroneously thought to be cancer on palpation, and even during an exploratory laparotomy.

(*d*) *Röntgenological Examination of the Pancreas*

This should prove helpful in the diagnosis of stone in the pancreatic duct (*sialolithiasis*), since the stones consist of lime salts. The technic has yet to be worked out in suitable cases.

4. Functional Examination of the Pancreas

We may test (a) the sufficiency of the functions of external secretion of the pancreas, and (b) the sufficiency of the functions of internal secretion.

(*a*) *Tests for the Sufficiency of the Functions of External Secretion*

Here we depend upon (1) the examination of the feces, (2) certain digestive tests (Sahli's glutoid test; Schmidt's meat-sack test), and (3) examination of the duodenal contents.

i. Special Examination of the Feces in Pancreatic Disease

English observers (Cowley, Lloyd and others), a century ago, called attention in pancreatic diseases, to the characteristic disturbances of absorption that lead to the appearance of meat and fat in the stools. Such stools are very bulky. The total amount of feces may exceed a kilo in weight, the dried residue amounting to 150 grams instead of the normal 30 grams. If the stool be formed, its diameter is large. Under the microscope, the field may be crowded with striped muscle fibers and fat droplets, and chemical examination reveals large amounts of nitrogen (6-15 grams N. per day). Fatty stools also occur in biliary obstruction, but the fatty pancreatic stools are characterized by a greater disturbance in the cleavage of fats, showing much more neutral fat than do acholic stools. Sometimes, so much fat is present that the stool, on cooling, looks like butter. Where imperfect assimilation of fat is suspected, but the stool is not wholly characteristic, typical "buttery stools" can sometimes be produced by feeding the patient, for one or two days, on oatmeal containing 250-300 grams of butter per day; in normal digestion, this amount of butter can be assimilated.

Microscopic examination of pancreatic stools shows, besides much neutral fat, many fatty acid crystals, rather than soaps (owing to the deficiency of alkali of the pancreatic juice). If the ordinary examination of the stool is suggestive of faulty assimilation of protein and fat, the assimilative powers may be exactly measured by placing the patient on the Schmidt-Strassburger test diet for two or three days and subjecting the fat in the feces to quantitative chemical analysis.

The methods used for qualitative and quantitative estimation of ferments in the feces (pepsin, trypsin, crepsin, amylase, maltase, lactase, lipase, enterokinase, etc.), can be applied, but are as yet of doubtful practical value. The methods used in testing for ferments have been described under Duodenal Contents and Feces.

ii. Digestion Tests for the Sufficiency of the Functions of External Secretion

Sahli's Glutoid Test.—In order to get direct evidence regarding the chemical activity of digestion within the intestines, Sahli has used glutoid capsules made from gelatine (glutoid), hardened in formaldehyd. Such capsules are not soluble in the gastric juice, but dissolve quickly in mixtures containing pancreatic juice. They are filled with substances that, after absorption, may be recognized in the saliva, or in the urine. Potassium iodid, iodoform, or salicylic acid may be used. Thus after the ingestion of 0.15 gram of iodoform, iodin could be detected in the saliva (or in the urine) in from 15-75 minutes. The iodin is detected by adding

1 c.c. of dilute H_2SO_4 and 0.5 c.c. of a 1 per cent solution of sodium nitrite to 10 c.c. of urine or saliva. To this, 2 c.c. of chloroform are added, and if iodin be present, the chloroform will assume a rose color.

If 0.5 gram of salol be taken in the glutoid capsule, salicylic acid can be detected in the urine with ferric chlorid within one and a half hours.

Glutoid capsules ready for use can be bought in the market (A. G. Haussmann, St. Gall, Switzerland). It is best to give the capsules with a test-breakfast and collect saliva, or urine, three hours after the administration, and at regular intervals thereafter, in numbered beakers. One must know that the gastric motility is normal, for motor insufficiency of the stomach might retard the entrance of the capsule into the intestines. When gastric motility is normal, the glutoid-capsule test gives us the resultant of the power of pancreatic digestion and the absorptive power of the intestine.

A useful modification of the test is to place a glutoid capsule in filtered duodenal contents, and note the time required for solution in the thermostat at 37°.

Schmidt's Nucleus Test.—The nuclei of muscle fiber are digested in the intestine by the pancreatic juice, not in the stomach. Fresh, lean beef is cut into cubic centimeter cubes and hardened in absolute alcohol. These cubes are enclosed in tiny bags of silk gauze and kept in alcohol, to be washed in water for a few hours before using.

The patient, placed on a Schmidt-Strassburger diet, swallows these bags daily for two or three days. The bags are recovered from the feces by diluting the latter with water and straining. The muscle fiber removed from the bag can be hardened, sectioned and stained, or can be teased in acetic acid, or in dilute methylene blue, and examined microscopically. Complete preservation of the nuclei indicates entire absence of pancreatic juice.

There are three sources of error; (1) in diarrhea, the bags may be passed through the intestine too quickly to permit of digestion of the nuclei; (2) when the bags remain too long in the intestine, the nuclei may be destroyed by intestinal bacterial action; (3) while trypsin, pepsin and erepsin cannot dissolve the nuclei, it sometimes happens that, in active gastric digestion, the muscle fibers are so completely digested that the nuclei are lost.

iii. Examination of the Duodenal Contents to Test the Functions of External Secretions

This has already been described under examination of the intestines (*q. v.*).

(*b*) *Tests for the Sufficiency of the Function of Internal Secretion of the Pancreas*

We get clews regarding the endocrin function of the pancreas (1) from the existence of a diabetes mellitus (if it be pancreatic in origin), or (2) from the experimental production of an alimentary glycosuria of pancreatic origin.

Pancreatogenous Diabetes mellitus.—Only a certain proportion of the cases of diabetes mellitus can be proven to be of pancreatic origin (acute pancreatitis; carcinomata; cysts; cirrhosis; lues; arteriosclerosis). When insufficiency of the external secretion of the pancreas (pancreatic stools, absence of ethereal sulphates in the urine) exists along with diabetes mellitus, we can be fairly sure that the diabetes itself is due to loss of the internal secretion of the pancreas. That cases of pancreatogenous diabetes occur from damage to the internal secretion of the pancreas, without damage to the external secretion, seems certain, but we do not know how positively to demonstrate this fact *intra vitam*.

Alimentary Glycosuria.—When physical signs of pancreatic disease exist, or when the feces point to disturbance of the external secretion, we may judge of the efficiency of the internal secretion of the pancreas by testing for alimentary glycosuria.

The patient is given 100 grams of glucose, dissolved in tea, two hours after breakfast, and the urine is examined every two hours until six hours have passed, and also at the end of twenty-four hours, for sugar.

Cammidge's Reaction (Osazone Test in the Urine After Treatment with HCl).—For a time, this test was believed to be of value in functional diagnosis of the pancreas, but it has turned out to be unreliable. Some years ago, I, personally, studied the reaction and found that the urine of normal persons sometimes yielded it. In my opinion, it is entirely unjustifiable to regard a positive Cammidge reaction as an indication for surgical exploration of the pancreas. The test, being of no value, will not be described here.

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J. Special Examination of the Liver, Gall-Bladder, and Biliary Passages

1. Anatomical Physiological Introduction

The liver (*hepar*) is the largest gland in the body. It lies chiefly in the right hypochondriac region, partly also in the epigastric and the left hypochondriac regions. In the right hypochondriac region, it extends upward as far as the lower margin of the fourth rib in the clavicular line. Its *anterior margin,* below, leaves the right costal arch at the clavicular line, to run obliquely upward and to the left; in the middle line, it occupies a level corresponding to the middle of the line joining the xiphoid with the umbilicus, and cuts the left costal arch at a point lying between the sternal and the parasternal lines on the left. Along this anterior margin is a notch, or incisure, the *incisura umbilicalis;* it is situated in the middle line and is for the ligamentum teres hepatis. Situated between the right parasternal and the right clavicular lines (just lateral from the right margin of the rectus muscle), is the fossa for the gall-bladder (*fossa vesicae felleae*). The anterior margin of the liver, in children, may extend 2 cm. below the right costal margin in the clavicular line.

On taking up the study of hepatic diseases the anatomy of the liver should be thoroughly reviewed, and the structural relations, especially the relations of the hepatic lobules to the bile ducts, on the one hand, and to the blood vessels, on the other, firmly grasped.

The **anastomoses between the portal system of veins and the system of the inferior vena cava** should be kept in mind, including:

(1) At the *cardia* of the stomach, between the coronary vein of the stomach (going to the vena porta) and the esophageal veins (going to the V. azygos). From these *esophageal varices,* severe and even fatal hemorrhage may occur.

(2) At the *rectum,* in the hemorrhoidal plexus, between the superior hemor-

rhoidal vein (going to the V. mesenterica inferior) and the middle and inferior hemorrhoidal veins (going to the hypogastric veins and inferior cava). Varices here are known as *hemorrhoids.*

(3) The *parumbilical veins of Sappey,* four or five small vessels connected near the navel with the superficial veins of the skin and the inferior epigastric veins and internal mammary veins (going to the vena cava), and, internally, connecting with the veins running in the ligamentum teres hepatis to the portal vein. The parumbilical veins, when enlarged, give rise to the so-called *caput medusae* seen in cirrhosis of the liver.

The **functions of the liver** consist in taking substances from the blood, transforming them, and excreting a part of them through the bile and returning a part (sometimes gradually) to the blood. The *bile,* though mainly an excretion of useless substances, is, to a certain extent, a secretion of importance for intestinal digestion. Moreover, a portion of the substances excreted through the bile into the intestine is reabsorbed into the blood, to be excreted by the kidneys (hydrobilirubin, ethereal sulphates, etc.). The liver cells play an important part in intermediary metabolism; indeed, the liver is the "central laboratory" of metabolism, and its chemical functions have been carefully studied experimentally (1) in the isolated living organ, (2) in extracts of the organ, and (3) by shunting out its activity through anastomosing the vena porta with the vena cava (Eck's fistula).

Only certain of the more important functions of the liver can be referred to here.

Relation of the Liver to Protein Metabolism.—Urea is formed largely in the liver, though to a certain extent in the other tissues. The ammonia resulting from the deaminizing of the amino-acids is transformed into urea by first combining with CO_2 to form carbaminic acid, which is then converted into carbamid (urea). In cases of acidosis due to lack of carbohydrate metabolism, this ammonia may be caught up out of intermediary metabolism and be excreted in the urine, along with diacetic acid, beta-oxybutyric acid, and acetone.

Relation of the Liver to Carbohydrate Metabolism.—The liver and the muscles are the parts of the body in which glycogen is chiefly warehoused. The glucose absorbed in digestion is synthesized in the liver to glycogen. This glycogen, in turn, is given over to the blood gradually, in small amounts, as needed, being mobilized from its depot by means of an amylase (glucase), which, apparently, is produced under the influence of sympathetic innervations they, in turn, being stimulated by epinephrin circulating in the blood.

The normal liver can convert fructose (levulose) first into glucose, and then into glycogen. In hepatic insufficiency, this function of the liver may suffer. One test for hepatic insufficiency consists in feeding levulose and observing whether an alimentary levulosuria (*q. v.*) appears or not.

It is probable that the liver can also make glycogen from the N-free residues of the amino-acids, from glycerin, and from fat.

Relation of the Liver to Fat Metabolism.—The liver can store up fat, but, compared with the subcutaneous tissues, it is insignificant as a fat depot. In disease, the fat content of the liver may be enormously increased, fat wandering in.

It is probable that fatty acid chains may undergo degradation, with formation of diacetic acid, in the liver, but the problems connected with fat metabolism require elucidation. (See Part XIII.)

Relation of the Liver to Iron Metabolism.—Iron of the food is stored up in the liver and gradually carried away from it in the white corpuscles. Degenerating red corpuscles undergo disintegration in the liver; the iron retained for further use by the organism and the iron-free derivatives of hemoglobin are given off as the coloring matter of the bile.

Function of the Liver in Rendering Poisons Inert (Detoxicating Function).—This is one of the essential and specific functions of the liver. Poisonous metals like arsenic and substances like nicotin are rendered inert in the liver. A number of organic substances, especially those arising from intestinal putrefaction (phenol, indoxyl, etc.) are rendered inert in the liver, by so-called "pairing" or conjugation with sulphuric acid, or glycuronic acid. Other poisons are oxidized.

Just what poisons are responsible for the toxic phenomena in hepatic insufficiency is not known. The symptom-complexes described as *hepatargia*, or *hepatic auto-intoxication*, can be produced experimentally by making an Eck's fistula in dogs fed on meat.

Bile Production.—The specific secretion of the liver cells is the bile, which amounts daily to about one kilogram. The secretion goes on continuously, though it is increased by eating, and especially by a fat-and-meat diet. The bile produced during fasting collects in the gall-bladder, but when acid chyme passes into the duodenum, the biliary passages are emptied reflexly into the intestine. The most important constituents of bile are *bilirubin* (derived from hemoglobin), the *biliary acids*, and *cholesterin*. In the intestine, the bilirubin is reduced to hydrobilirubin (urobilin), part of which is discharged with the feces, part reabsorbed. Of the latter, a part is re-converted in the liver into bilirubin and again given off in the bile ("circulation of the bile"), and a part is excreted in the urine as urobilin.

The part played by the bile in intestinal digestion is very complicated, and, in some ways, obscure. The bile contains no ferments except a small quantity of *amylase*. Its principal digestive function appears to be its *action on fats*. The salts of the biliary acids energetically activate lipase, and, to a less extent, trypsin. As soon as minute amounts of fatty acids are formed, these, with the salts of the biliary acids, give rise to soaps, which in turn convert fats into a very fine emulsion, thus favoring the cleavage of fats. The bile *precipitates the pepsin* of the chyme in the duodenum, preventing it from destroying trypsin and erepsin. The bile is also a normal *stimulus to intestinal peristalsis*.

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2. Symptoms of Hepatic Disease

Among the symptoms met with in hepatic diseases, the more important are (a) pain, (b) jaundice, (c) cholemia, (d) intestinal hypocholia, or acholia, and (e) fever of hepatic origin. In addition to these, we are often helped by the finding of (f) alterations in the size of the liver, (g) signs of portal obstruction (hemorrhoids, hemorrhage from esophageal varix, ascites, enlarged spleen), (h) toxic cerebral symptoms (due to cholemia), or (i) evidences of infection (fever, chills, sweats, leukocytosis).

(*a*) *Hepatic Pain*

This may be due either to stretching or inflammation of Glisson's capsule or to contraction of the walls of the gall-bladder (cholecystitis, gall-stone colic). Pain arising in the liver often radiates to the right shoulder. One of the commonest causes of pain in the right hypochondrium is stretching of the capsule in passive congestion of the liver due to cardiac insufficiency; in such cases, the liver is often tender on palpation.

(*b*) *Jaundice or Icterus*

The yellow staining of the tissues (skin, sclerae, mucous membranes) is due to bile pigments in the blood (*bilirubinemia*), and their deposition therefrom. It is usually associated with *bilirubinuria* (yellow foam; Gmelin's test) and with clay colored feces (*intestinal hypocholia,* or *acholia*).

Bile pigments, formed by the liver cells, pass over into the blood through the lymphatics as a result of obstruction in the biliary passages. This obstruction may affect either the large extrahepatic bile vessels (ductus choledochus, ductus hepaticus), or the small intrahepatic bile vessels (interlobular vessels, bile capillaries). The obstruction in the biliary passages may be due (1) to *compression of the ducts from with-*

out (tumors, scars, swollen liver cells, or dilated liver capillaries), (2) to *alterations of the walls of the vessels* (inflammations, neoplasms), (3) to *stopping of the lumen* of the vessels (stones, mucus, parasites), or (4) to *thickening of the bile* (especially when hemolysis is increased). When hemolysis is increased coagula may form in the minute bile capillaries owing to the excretion of protein with the bile (*albuminocholia*). Increased hemolysis gives rise to an increased bilirubin content of the bile (*pleiochromia*) rather than to an increased quantity of bile (*polycholia*). According to Chauffard, when a jaundice is hemolytic in origin, there is increased fragility (hyporesistance) of the red blood corpuscles, and many granular red blood corpuscles and microcytes are present in the blood. The jaundice of the newly born (*icterus neonatorum*) and the so-called family jaundice (*congenital hemolytic icterus*) are probably hemolytic in origin. Some maintain that, owing to a faulty function of the liver cells, bile, at the moment of secretion, may go back into the blood rather than into the biliary passages, but this view is at present in disfavor.

When a jaundice is due, not to increased hemolysis, but solely to obstruction in the biliary passages, it is called *obstructive jaundice* or *hepatogenous jaundice*. When it depends upon increased hemolysis it is also obstructive and hepatogenous (coagula in minute bile capillaries), but, on account of the associated hematogenous factor, is spoken of as *hemohepatogenous*, or as *hemolytic, jaundice*.

Obstruction to the biliary passages may be partial or complete; in *complete obstruction*, no hydrobilirubin will be formed in the intestine, and urobilin will disappear from the urine, while bilirubin will be present in the urine in large amounts. In *partial obstruction* both bilirubin and urobilin are present in the urine. In some cases of jaundice, urobilin is present in the urine without bilirubin (so-called *urobilin-icterus*). In such cases the staining of the tissues is not really due to urobilin but to bilirubin, the increased urobilin excretion in the urine being due to increased formation of hydrobilirubin in, and absorption from, the intestine. Increased excretion of urobilin in the urine may occur without jaundice, especially in certain liver diseases (chronic passive congestion, cirrhosis); this phenomenon probably depends upon a disturbance of liver function, in that the liver is unable to convert its normal quota of reabsorbed urobilin into bilirubin. If urobilin have been absent from the urine in jaundice and then begin to appear, this may point to a letting up of the obstruction in the biliary passages.

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(*c*) *Effects of Bile in the Blood* (*Cholemia*)

Besides the staining of the tissues (icterus), other phenomena result from the absorption of bile into the blood, especially certain functional disturbances of the vascular, nervous, muscular, renal, and cutaneous systems. These include bradycardia, slowed clotting time of the blood, hemorrhagic diathesis, cerebral disturbances (depression or irritability, headache, insomnia, hypothermia; sometimes delirium, convulsions, coma), asthenia, xanthopsia (seeing yellow), hemeralopia and nyctalopia (day and night blindness), pruritus, urticaria, bilirubinuria, albuminuria and cylindruria.

The term *cholemia* is sometimes reserved for the severer cerebral disturbances, and it has been assumed that, in the cases exhibiting them, we have to deal not exclusively with intoxication from absorbed bile, but also with the results of disturbed liver cell activity, the so-called *hepatic insufficiency* or *hepatargia.*

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(*d*) *Effects of Absence of Bile from the Intestine* (*Intestinal Hypocholia, or Acholia*)

Clay colored stools appear, owing to faulty assimilation of fats and absence of bile pigments. The foul feces and the flatulence, so common in jaundice, are due to abnormal fermentative processes in the intestine.

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(e) *Fever of Hepatic Origin*

In hepatic disease, fever may point to the cholangitis complicating cholelithiasis, to abscess of the liver, to carcinoma, or to lues. Intermittent fever with chills, sweats and jaundice is tolerably characteristic of stone in the common bile duct, with infectious cholangitis.

3. Physical Examination of the Liver and Gall-bladder

By far the most important method of examination here is palpation, though percussion, and, to a slight extent, inspection and auscultation, may, in some cases, be helpful.

(a) *Palpation of the Liver and Gall-bladder*

When the abdominal wall and the liver are normal, the *liver* is not palpable by any method. In emaciation, and especially when the abdominal wall is flaccid, or when diastasis of the recti exists, the upper surface and the anterior margin of the liver may become palpable, especially if there be any increase in its consistence. The child's liver is usually distinctly palpable (both upper surface and anterior margin). The normal *gall-bladder* is not palpable, though, occasionally, in especially favorable cases, the fossa for the gall-bladder can be made out.

In pathological cases, the liver and the gall-bladder often become palpable.

To palpate the anterior margin and the lower surface, including the gall-bladder, the *thumb method of Glénard* is advised. The patient lies on his back, the physician sitting to his right on the edge of the bed. In palpating, both hands are used, the intention being to press the mass of intestines upward and so direct the anterior margin of the liver toward the abdominal wall. To accomplish this, the right hand is so placed, at first, that the fingers lie obliquely lateralward and below (toward the inguinal fold), and the base of the hand below the navel; this hand, with the wrist as a center, is now rotated so that the fingers pass from an oblique position into a transverse position, or so as to be directed obliquely upward. With the ball of the left thumb in the right hypochondrium, pressure is then exerted below the anterior margin of the liver, and when the patient takes a deep breath, the anterior margin and the lower surface of the liver are palpated with the thumb as they descend.

The anterior margin of the liver can sometimes be well felt by *Devoto's method.* The patient is asked to stand up, and the physician, standing behind him and encircling the body with his arms, palpates with both hands in the hepatic region.

Dislocation of the liver may result from a low position of the diaphragm (right-sided empyema, pleuritis, pneumothorax), or from subphrenic abscess (diaphragm high), or from relaxation of the suspensory ligament (wandering liver).

Alterations in the form of the liver are seen in visceroptosis, in corset liver, and in the linguiform lobulation of the liver known as Riedel's lobe, and due partly to adhesions between the gall-bladder and the under surface of the liver.

True enlargement of the liver is met with in cardiac insufficiency (chronic passive congestion), in biliary obstruction (icteric liver), in fatty liver, liver abscess, lues, amyloid, neoplasm, echinococcus, hypertrophic cirrhosis, and leukemia.

When the liver is enlarged, its consistence should be determined, and also the character of its surface and anterior margin, and one should ascertain whether or not the spleen is at the same time enlarged.

The large liver is painful in passive congestion, in abscess, and sometimes in echinococcus, acute yellow atrophy, carcinoma, lues, and cirrhosis. There is no pain when enlargement is due to a fatty, or an amyloid, liver.

The **consistence of the enlarged liver** is abnormally firm in the cirrhoses, in multilocular echinococcus, in carcinoma, and especially in amyloid; it is soft in liver abscess, in fatty liver, and in unilocular echinococcus (hydatid thrill palpable).

The *anterior margin* is rounded in passive congestion, in fatty liver, and in amyloid; it is often uneven in cirrhosis, in lues, and in carcinoma.

The *surface* of the large liver is smooth in passive congestion, in biliary obstruction, in hypertrophic cirrhosis, and in fatty and amyloid livers; it is nodular in carcinoma, in lues, and, sometimes, in abscess; in atrophic cirrhosis it may be more evenly granular.

Most conditions that cause enlargement of the liver also enlarge the spleen, but carcinoma hepatis and fatty liver are marked exceptions to this rule.

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(*b*) *Inspection of the Liver and Gall-bladder*

When the liver is markedly enlarged, the lower portion of the thorax may look expanded, and there may be bulging in the epigastrium. Sometimes, the anterior margin of the liver can be seen moving up and down beneath the abdominal wall during respiration. Occasionally, a distended gall-bladder may be visible when the abdominal walls are thin.

Hepatic pulsation may sometimes be visible as well as palpable (*e. g.*, in tricuspid insufficiency).

Litten's sign may be present when the liver is pressed downward by a subphrenic abscess, while it is absent in depression of the liver due to pneumothorax, or to empyema.

(c) *Percussion over the Liver and the Gall-bladder*

The portion of the liver in direct contact with the abdominal wall yields absolute dullness on light percussion. The upper part of the liver, separated from the thoracic wall by the lung, yields relative dullness on strong percussion. *The determination of the latter is too uncertain to be of any clinical value.* When it is desired to determine the level of the upper limit of the liver this should be done by x-ray examination. In amebic abscess, especially, röntgenography may reveal a bulging prominence on the upper surface.

The **absolute liver dullness** is identical above on the right side with the lower lung limit; on the left side, it is continuous with the cardiac dullness and not delimitable therefrom. The lower limit of liver dullness corresponds to the position of the anterior margin of the liver.

Normally, the *upper limit* of absolute liver dullness is, at the spine, opposite the 11th rib; in the scapular line, at the lower margin of the 9th rib; in the axillary line, at the lower margin of the 7th rib; in the mammillary line, at the 6th intercostal space; and, in the parasternal line, at the 6th rib. The *lower limit* of liver dullness corresponds, in the scapular line, to the 11th rib; in the axillary and the mammillary lines, to about the costal margin; and in the middle line, to a level midway between the xiphoid and the umbilicus, from which point it passes obliquely upward toward the apex of the heart, cutting the left costal margin between the left parasternal and the mammillary lines on the left side. In the right parasternal line a small convex area of dullness corresponding to the *gall-bladder* may project downward from the liver dullness. Distension of the stomach and of the intestine often make the determination of the lower margin of absolute dullness difficult. On deep inspiration, the upper margin of absolute liver dullness moves downward (descent of the lung). Enlargement of the liver lowers the lower limit of absolute dullness; diminution in the size of the liver lifts the lower limit of absolute dullness; indeed the absolute dullness may entirely disappear in atrophy, or in cirrhosis, of the liver.

Widening of the absolute liver dullness occurs in all conditions that render the anterior margin of the liver palpable (*q. v.*) The upper limit of absolute dullness may occupy a higher level in tumors, cysts, or abscess of the liver; the absolute liver dullness, at its upper margin, may become continuous with the absolute dullness due to a subphrenic abscess or to intrathoracic processes like pleural effusion and pneumonia.

Diminution of the absolute liver dullness may be due (1) to disease of the liver itself (cirrhosis, acute yellow atrophy, etc.), (2) to the presence of air in the peritoneal cavity between the liver and the anterior abdominal wall (perforative peritonitis), or (3) to the interposition of the colon or small intestine between the liver and the surface.

An abnormal size of the liver dullness may coexist with a liver of normal size; thus, rotation of the liver on a transverse axis may cause *retroversion* with lessened dullness (emphysema, kyphosis), or *anteversion* with widened dullness (thorax paralyticus, habitus enteroptoticus).

(*d*) *Auscultation of the Liver and Gall-bladder*

Occasionally peritoneal friction is audible, as well as palpable, over the liver. Now and then, in cholelithiasis, one may hear, on palpation, in the gall-bladder region, a grating sound due to the rubbing of the gall-stones on one another.

(*e*) *Exploratory Puncture of the Liver*

This is rarely resorted to now, since exploratory laparotomy has become so general. It was formerly employed for the diagnosis of hepatic abscess and of echinococcus cysts.

(*f*) *Röntgenology of the Liver and the Biliary Passages*

Liver.—In making *röntgenograms of the liver,* the anticathode of the x-ray tube should be placed behind, in rather a high position, opposite the 6th and 7th thoracic vertebrae, and the rays directed obliquely (in a craniocaudal direction) to the plate over the hepatic region in front. The rays then penetrate the liver in its greatest diameter, and it is usually possible to show the lower surface of the liver well, especially if the large intestine be first partially distended with air.

Fig. 391.—X-ray of the Gall-bladder Showing Many Small Facetted Stones. More Than 70 Gall-stones Were Removed at Operation in This Case. (After C. G. Barkla, Arch. of the Röntgen Rays.)

In examining the upper surface of the liver for amebic abscess or neoplasm, or in searching for subphrenic abscess, *röntgenoscopy* during movements of respiration may be helpful. Sometimes, it may be desirable, in order to get a distinct outline of the superior surface and the lateral region of the liver, to inject, under aseptic precautions, some pure oxygen gas into the peritoneal cavity. This is very easy if there be ascites. The gas tends to accumulate beneath the dome of the diaphragm and at the side of the liver; röntgenoscopy or röntgenography may then be undertaken.

Gall-stones.—Röntgenograms of gall-stones were long unsuccessful, chiefly because (1) pure cholesterin stones scarcely cast any shadow, and (2) röntgenologists had not developed the special technic necessary.

The patient should be carefully prepared beforehand. The intestines should have been cleansed thoroughly on the day preceding the examination, and the röntgenogram made in the morning, fasting. The patient lies on the abdomen with the large plate in front of him over the gall-bladder region. The upper part of the body is supported by cushions so that the thorax is shoved strongly backward. This brings the gall-bladder closer to the plate. A compression diaphragm is applied perpendicularly to the plate, and the anticathode so placed, behind, that the normal radiation passes directly through the gall-bladder and opening in the diaphragm to the plate. Very soft tubes, and the shortest possible exposure, when the breath is held, should be used. There is some difference of opinion as to the advantage or disadvantage of an intensifying screen. It may be of value to make several röntgenograms and to superimpose two or three of them, examining them carefully against the sky. A pair of stereoscopic röntgenograms sometimes aids materially in the detection and interpretation of doubtful shadows.

With this technic it is possible, in a fair proportion of cases, to get *direct evidence* of the presence of biliary calculi. Great care must be taken, however, to differentiate a gall-stone from a renal calculus or from other calcified body in this region, such as a calcified costal cartilage. I have known one patient to be operated upon for renal calculus when the shadow was really due to a gall-stone, and a mistake in the other direction is still more often made.

Biliary calculi are more distinct and appear smaller on the plate when the plate is placed on the abdomen than when it is placed at the back, while the opposite is true of renal calculi. By taking two plates and shifting the tube five inches between exposures, the exact distance of the calculus from the anterior abdominal wall can be determined.

A gall-stone, if it have a cholesterin nucleus and a calcified outer coat, may cast a ringlike shadow. This is rarely seen in a renal stone. Further, if several gall-stones be present, the facetted surfaces may be visible in the röntgenogram, while if several renal calculi be present, one is usually larger than the others, or the branchlike appearance of a large calculus may be visible.

Evidences of Cholecystitis with Adhesions.—It may be more important, when considering surgical operation, to know whether a cholecystitis with adhesions exists, with or without stones, than to know, merely, whether a biliary calculus is present or not. The presence of a gall-stone, without associated cholecystitis, is not necessarily an indication for operation, whereas the existence of a cholecystitis with adhesions requires operation whether a stone be present or not.

Judgments from röntgenograms, regarding adhesions about the gall-bladder, are based upon deformities of the duodenal cap, of the pyloric region of the stomach, or kinking and constriction of the flexura coli dextra. It may, however, be very difficult to differentiate such an adhesive pericholecystitis from adhesions and cicatricial contractions due to pyloric or duodenal ulcer. Fortunately, however, the differentiation is practically less important than it would be if surgery were not indicated in both instances. Röntgenologists agree, however, that the adhesions

in gall-bladder infection are more extensive than in ulcer; even the greater curvature may be involved and the stomach is drawn over to the right, with "hepatofixation" and angulation of the cap. Usually the pyloric end of the stomach is as much involved in the adhesions as is the cap; besides, one sees no signs of a localized area of induration in the cap, and narrowing of its lumen is less frequent than in ulcer of the duodenum.

It must be strongly emphasized that negative x-ray findings by no means rule out the existence of gall-stones or of infective cholecystitis. The clinical history may be so definite that surgical operation is indicated even when the röntgenological evidence is entirely negative.

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4. Functional Testing of the Liver

From time to time, various procedures have been devised to test the functional capacity of the liver, but, as yet, no single test has been found that meets all the requirements.

Until recently, nearly all so-called liver function tests were based upon the part the liver plays in carbohydrate metabolism, namely, (a) the conversion of the monosaccharides, dextrose, levulose and galactose, into a polysaccharide, glycogen; (b) the storage of the glycogen as such, and (c) the reconversion of it into dextrose to supply the needs of the body elsewhere.

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(*a*) Carbohydrate Tests of Hepatic Function

Alimentary Levulosuria.—The test, which was introduced by Strauss, and bears his name, consists in the ingestion of 100 grams of levulose into an empty stomach, and the examination of the urine voided during the following 4-6 hours for the presence or absence of this sugar. For the latter procedure, Fehling's and Seliwanoff's tests are used. According to Strauss, the appearance of levulose in the urine, under the conditions of the test, indicates a diminished functional capacity on the part of the liver.

Alimentary Galactosuria.—Bauer's test is similar to that of Strauss except that 30 grams of galactose are used instead of 100 grams of levulose.

These two, perhaps the most widely used of the carbohydrate tests, are by no means entirely satisfactory. In the first place, there are technical difficulties such as nausea and vomiting on the part of patients after the ingestion of such large amounts of sugar. Again, the results obtained have not been particularly gratifying, so that comparatively little real value attaches to them.

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(*b*) *Urobilinogenuria as a Test of Hepatic Function*

The presence of urobilinogen in the urine has been considered by some workers to be indicative of liver disease, or of liver injury. The recent comprehensive work of Wilbur and Addis makes this view seem very unlikely, since they have shown conclusively that observations on a single or a 24-hour specimen have no significance, and that only where repeated observations are made over a period of at least two weeks, and then only when control studies of the feces have been made to exclude blood destruction as a factor in the production of urobilinogen, can the findings be accepted as evidence of loss of functional power of the liver.

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(*c*) *The Fibrinogen Content of the Plasma*

Whipple has suggested that the determination of the amount of fibrinogen present in oxalated plasma may be used as a test of liver function. The *heat-coagulation method* as described by him is suggested for these determinations. This method consists in the heating of a known quantity of oxalated plasma at 59° C. for 20 minutes, during which time all the fibrinogen is coagulated. The material is then centrifuged at high speed, washed with water, centrifuged, washed with alcohol and brought into a Gooch crucible with the aid of a filter pump. It is then dried in the crucible and weighed, the empty crucible having been weighed first. Values below 350 milligrams per 100 c.c. oxalated plasma (50 c.c. fresh blood + 5 c.c. oxalate solution) may be regarded as abnormal. Studies carried out by Rowntree, Marshall and Chesney indicate that this test may prove to be of distinct value, since it was positive in 8 patients, 6 of whom were supposed to have cirrhosis of the liver, clinically, and one to have been an enlarged liver, due to chronic passive congestion dependent upon myocardial insufficiency. The other

case was one of splenomyelogenous leukemia, and a second determination, carried out upon this patient, gave a perfectly normal value.

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(*d*) *The Fibrinolytic Ferment of the Blood*

Goodpasture has found that in some cases of cirrhosis of the liver, there is present, in the blood stream, a ferment that dissolves fibrin, that is to say, will dissolve a blood clot. The ferment is specific for fibrin, does not attack fibrinogen, is destroyed by heating at 56° C. for 30 minutes, and is easily recognized.

Blood is drawn aseptically from a vein of the forearm by means of a needle and syringe, and allowed to stand in a sterile glass tube, whereupon the clot forms as normally. If this clot be allowed to stand at 37° C. for several hours, and if the ferments be present, at the end of 6-8 hours it will be found, on examination, that the clot has entirely dissolved.

It would seem that this ferment, when present, has definite diagnostic significance, since it was present in 7 cases of cirrhosis of the liver and was not found in any other condition in a series of 45 cases studied by Rowntree, Marshall and Chesney.

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(*e*) *The Lipase Content of the Blood as an Index of Hepatic Function*

The determination of the lipolytic activity of the blood has been suggested by Whipple as an index of liver function. By lipolytic activity is meant the capacity of the blood to decompose ethyl butyrate by enzymatic activity when the substances are allowed to stand at body temperature for 24 hours. The method used is that devised by Loevenhart and is as follows: 1 c.c. of serum, or of oxalated plasma, is added to 0.26 c.c. ethyl butyrate, the mixture is then diluted with water to 4 c.c., placed in stoppered test tubes, and incubated at 37° C. for 20-24 hours. The amount of acid produced is then determined by titration with $\frac{N}{10}$ NaOH, azolitmin being used as indicator. Control tubes are set up without ethyl butyrate and are titrated with $\frac{N}{10}$ HCl in order to determine the alkalinity of the blood, for which correction must be made. The results are expressed in terms of $\frac{N}{10}$ alkali. The upper limit of normal may be regarded as 0.40 c.c. of $\frac{N}{10}$ alkali, values above that being supposed to indicate liver injury. This test has not proved to be of any definite value and is not likely to be used to any great extent.

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(f) Excretion of Phenoltetrachlorphthalein as a Test of Hepatic Function

This drug has been introduced by Rowntree, Hurwitz and Bloomfield as a test of liver function. It is similar in chemical constitution to phenolsulphonephthalein, the drug used in testing renal function, but should not be confused with it. It differs from it in that the sulphone groups are replaced by chlorin atoms, and, also, in its mode of excretion. In healthy persons, the drug is excreted in the bile, into the intestinal tract, and practically never appears in the urine.

The method, as devised by Rowntree, consists of three procedures; (1) the intravenous injection of 400 milligrams of the drug in freshly prepared, sterile solution, which has been filtered under aseptic precautions; (2) the collection of the feces over a period of 48 hours, the patient being purged in order to ensure complete elimination; and (3) the determination of the amount of drug excreted, which is carried out as follows: The total feces for 48 hours are diluted, in a large bottle (2 liters capacity), with water to 1 *l.* or to 2 *l.* if necessary, then shaken on a shaking machine until as homogeneous a mixture as possible has been obtained. One-tenth of this mixture (100 c.c. or 200 c.c. as the case may be) is removed, and to it is added 5 c.c. of 40 per cent NaOH. If the drug is present, the mixture assumes a reddish purple color. One then dilutes this second portion to 1 liter in a Florence flask, shakes well, transfers 100 c.c. to a small Erlenmeyer flask; and adds 5 c.c. basic lead acetate solution (saturated), which precipitates the bile pigments and gives to the solution a dirty, grayish white, color.

One has then simply to add 5 c.c. of 40 per cent NaOH and the drug goes into solution again, the characteristic color returning. This mixture is diluted to 200 c.c., filtered, and is then ready for comparison with a standard solution made at the time the drug is injected. For this comparison, the Rowntree-Geraghty modification of the Autenrieth colorimeter is used, the result being read off as per cent of the drug injected. An excretion of the drug in the feces in amounts less than 30 per cent of that introduced, or its excretion in the urine, will almost never be found in normal persons.

The work of Rowntree and his co-workers, who have studied the behavior of this drug in 113 persons, a number of whom possessed definite clinical evidence of anatomically diseased livers, indicates that this may prove to be of distinct value as an index of the presence, and to a less degree, of the extent, of liver injury.

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(*g*) *Nitrogen Metabolism and Hepatic Function*

The occurrence of disturbances in the nitrogenous metabolism in disturbances of the liver has long been known, especially the excretion of amino-acids (leucin, tyrosin, phenylalanin, etc.) in the urine in acute yellow atrophy and in phosphorus poisoning. In the series of 45 cases mentioned above, Rowntree, Marshall and Chesney have found definite disturbances of the nitrogen partition, both in the blood and in the urine. The evidence points to a relatively low urea per cent of the total non-protein nitrogen of the blood and a high amino-acid content of the same, together with a relatively low urea per cent in the urine and a high NH_3 and amino-acid output. More observations will have to be made before the exact relation of the nitrogen metabolism to the liver, particularly in disease, will be established, but it would seem that we may expect to find definite disturbances of the nitrogenous metabolism in cases of liver injury, especially a low urea per cent of the total non-protein nitrogen of the blood.

It may be said that all of these tests of liver function are of value when positive, but when negative, they do not exclude the presence of hepatic disease. It is too early to form an ultimate judgment of their value, but the field is promising, and one in which clinicians will doubtless continue to work, for we must study diseased organs from a physiological as well as from an anatomical point of view.

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K. Special Examination of the Peritoneum and Mesentery

On examining the peritoneum we keep in mind the possibilities of (1) peritonitis including subphrenic abscess, (2) ascites, (3) pneumoperitoneum and (4) neoplasm.

We note carefully the presence or absence of pain, tenderness, muscle spasm, tumor, dullness, or fluctuation, and pay attention to any coexistent constitutional manifestations (fever, leukocytosis).

The methods of examination have been described above, under General Examination of the Abdomen.

Part VIII

Section II

SPECIAL DIAGNOSIS OF DISEASES OF THE DIGESTIVE APPARATUS

A. Special Diagnosis of Diseases of the Mouth Cavity

The principal diseases met with here are:

I. Certain malformations (hare lip and cleft palate).

II. Certain diseases of the mucous membrane of the mouth, especially the different forms of stomatitis; and certain tumors (sarcoma or epulis, epithelioma of the lip, carcinoma of the tongue).

III. Certain diseases of the teeth, including dystrophic developmental changes (rickets, hereditary lues), dental caries, peridental abscesses, and diseases of the gums (tartar formation, pyorrhea alveolaris).

IV. Diseases of the salivary glands, especially parotitis, ranula, mixed parotid tumor, and Mikulicz's disease.

Here we shall discuss certain only of these diseases, especially those important to the practitioner.

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1. Inflammations of the Mucous Membrane of the Mouth (Stomatitis)

Definition.—By *stomatitis* is meant a general inflammation of the mucous membrane of the mouth. Special names are given to localized inflammations: of the lips (*cheilitis*), of the tongue (*glossitis*), and of the gums (*gingivitis*).

(*a*) *Catarrhal Stomatitis*

Etiology.—Dental caries; false teeth; alcoholism; infections; scurvy; mercurial treatment.

Symptoms.—Hyperemia; sore mouth; swollen, spongy gums; swollen tongue, showing markings due to teeth; heavy paste in mouth; salivation; fetid breath; difficulty in chewing and swallowing; swollen lymph glands.

(*b*) *Ulcerative Stomatitis*

This is often epidemic among children and the aged, especially in institutions.

Symptoms.—They are like those of catarrhal stomatitis, but much more severe. Ulcers develop on the gums and mucous membrane of the cheeks. Marked general disturbance, usually with fever. In hemorrhagic forms, the possibility of an acute leukemia should be thought of and a careful blood examination made.

(*c*) *Aphthous Stomatitis* (*Canker*)

Symptoms.—Spots the size of a pin's head, or larger, appear, first as vesicles; these rupture to form small ulcers with grayish white base and bright red margins. The affection is most common in infancy, though sometimes seen in adults. It may easily be confused with a herpes of the mucous membrane.

There is pain, salivation, and swelling of the lymph glands.

The disease is benign and easily differentiated from luetic lesions and from thrush.

(*d*) *Gangrenous Stomatitis* (*Noma*)

This rare disease may occur in children, especially after measles. There is rapid necrosis of the mucous membrane of the cheek, often spreading widely, and usually terminating fatally (sepsis, or pneumonia).

(*e*) *Parasitic Stomatitis or Thrush* (*Soor*)

Etiology.—See the Fungi of Thrush in Section on the Infectious Diseases.

Symptoms.—Milk-white deposits appear on the reddened mucous membrane of the mouth and throat, and, sometimes, on the esophagus. The disease is prone to occur in feeble little children, and in adults who are seriously ill (pulmonary tuberculosis; carcinoma; typhoid). Under the microscope, a mycelium of doubly-contoured threads and scattered oval spores are visible.

The patients complain of dry mouth, dysphagia, and digestive disturbances.

Diagnosis.—This is easy on microscopic examination (characteristic fungi). It must be differentiated from *aphthous stomatitis* (absence of fungus; salivation).

(*f*) *Phlegmonous or Purulent Stomatitis*

Etiology.—It may be caused by various bacteria (streptococcus, staphylococcus, gonococcus). It arises from the infection of small wounds.

Symptoms.—Marked swelling and edema; salivation; pain; abscess formation. Sometimes the floor of the mouth is especially involved, causing swelling between the jaw and the hyoid bone (*angina Ludovici*), with dysphagia, dysarthria, and sometimes asphyxia; this form is often fatal.

(*g*) *Tropical Stomatitis* (*Sprue; Psilosis; Cochin China Diarrhea*)

Definition.—A peculiar afebrile affection of the mouth and gastro-intestinal tract, associated with (1) gastro-intestinal catarrh, which causes periodic diarrhea, and (2) diminution in the size of the liver. In the Northwestern States a disease described as nursing sore mouth (*stomatitis materna*), affecting both mother and child, seems to be similar though less malign. Whether the "hill diarrhea" of India, or "Simla trot," is a form of sprue, has not been decided.

Etiology.—The cause is, as yet, not known. Europeans who have been long in the tropics are most often affected. Castellani has studied moulds of the genus *Monilia* in the stools of sprue; he holds them responsible for the excessive gas production, but does not regard them as the cause of the disease. The relations of *Monilia* to sprue have recently been studied by Ashford in Porto Rico.

Symptoms.—The onset is insidious. The mouth begins to be sensitive, and there is a feeling of epigastric fullness. Morning diarrhea, alternating with periods of constipation, is common. The stools are bulky, putty-colored, frothy, and offensive; they excoriate the anus. Microscopically, the stools are acid, contain fat, fungi, and undigested food.

As the disease progresses, the tongue becomes very red at the sides and tip, and the surface glistening. Shallow ulcers may appear on the tongue and mucous membrane of the cheek. Small ulcers, known as Crombie's ulcers, near the posterior molars, are especially characteristic.

Rawness of the esophagus is complained of. The patient emaciates; the liver dullness diminishes; the abdomen is tympanitic. There is marked indicanuria. A marked secondary anemia develops with low color index, but with leukopenia and relative decrease of the polymorphonuclear elements in the differential count.

Diagnosis.—The disease must be differentiated (1) from *thrush* (typical membrane formations containing fungi; non-tropical; absence of sprue stools); (2) from *pellagra* (cutaneous manifestations characteristic; absence of sprue stools).

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(*h*) *Chronic Stomatitis*

Chronic irritation of the mouth (tobacco smoking) sometimes leads to sharply circumscribed, bluish-white areas known as *leukoplakia oris,* or, sometimes, as *buccal psoriasis,* or *buccal ichthyosis.* Many of the patients have had lues. Epithelioma sometimes starts in such a patch.

(*i*) *Luetic and Other Specific Forms of Stomatitis*

Primary chancres, mucous patches, or tertiary ulcers may appear in the mouth. Smooth atrophy of the base of the tongue is common in tertiary lues. Tuberculosis and actinomycosis of the tongue are rare. Through the courtesy of Dr. H. C. Buswell of Buffalo, I have had the opportunity of studying a blastomycetic nodule of the tongue that closely resembled carcinoma until the histological and parasitological study of a piece excised for diagnosis revealed its true nature.

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2. Neoplasms About the Mouth

(*a*) *Epulis*

Sarcomata, or fibromata, appear as small, pea-shaped, or walnut-shaped tumors on the margin of the gum (*epulis*). Some of them arise from the periosteum and are giant-celled sarcomata.

(*b*) *Epithelioma of the Lip*

This often appears as a chronic ulcer with hard base, and it may be hard then to distinguish it from a chancre. If, on pressure, small, whitish plugs can be squeezed out, found under the microscope to consist of flat epithelium, it is a chancroid. If the base has an even, reddish, lacquered look, from which no plugs can be squeezed, it is probably a chancre (Wassermann reaction; spirochete examination). The lymph glands are always enlarged in chancre, but may not become enlarged for months in epithelioma.

Caution! A complaint of a scaling, easily bleeding spot on the lower lip, continuing for months, means probably a malignant growth.

(*c*) *Cancer of the Tongue*

(*Carcinoma linguae*)

Every ulcer on the tongue, or near the tongue, must be regarded as suspicious. A firm, small nodule, especially if the tissues close by are slightly retracted, requires immediate operation. Any thickening appearing in an old leukoplakic spot is suspicious. Cancer at the posterior part of the tongue margin, opposite the tonsil, is often overlooked, Males, over forty, are most often affected.

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3. More Important Diseases of the Teeth and Gums

(*a*) *Dental Caries*

Definition.—A destructive process involving the enamel and dentine of the teeth.

Etiology.—Predisposing causes include (1) developmental anomalies of the enamel, (2) faulty position and articulation of the teeth (heterodontia), (3) the eating of food, poor in lime, and so soft as not to require

prolonged mastication, and (4) failure to cleanse the teeth properly after meals, and especially at bedtime.

The actual exciting cause is chemical action; the lime salts are dissolved out by acids, and the organic part of the tooth is digested by enzymes; both the acids and the enzymes are the product of bacterial growth in food residues in the mouth and between the teeth. The administration of HCl for medical reasons may also injure the teeth.

Symptoms.—No pain is felt until the enamel (substantia adamantina) has been injured in its whole thickness, and the dentine (substantia eburnea) is exposed to mechanical, chemical and thermal stimuli; the odontoblasts of the dentine transmit such stimuli directly to the sensitive pulpa dentis. As the caries extends, and the odontoblasts are injured, the pain grows less.

Objectively, if the smooth surface be attacked, the transparency disappears, the part becoming dull, opaque, white, and later ashy gray or brown. Or a black spot may be the first visible sign.

Diagnosis.—Diagnosis is easy when the caries is visible as on the labial, lingual, and masticating surfaces of the teeth. It may long be overlooked if the facies contactus is involved, but a dentist will find the defect by palpation with a curved probe. It is exceedingly important that a careful dental examination be made at least every three months for prophylactic reasons. The use of a very stiff brush, after dental floss, every night at bedtime tends to prevent caries and pyorrhea alveolaris.

(*b*) *Pulpitis, Periodontitis, and Dental Sepsis*

Definitions.—By *pulpitis* is meant an inflammation of the pulpa dentis; it is usually secondary to dental caries. By *periodontitis* is meant an extension of an infective pulpitis through the root canal (canalis radicis dentis) and the apical foramen (foramen apicis dentis) to the periodontium. It is very common around "dead teeth" in which the pulp has been killed, though the tooth maintains a low grade of metabolism by means of the living periodontium, which connects it with the alveolar periosteum. Infections starting from the apex of a tooth can give rise to various acute processes, such as *periostitis, alveolar osteomyelitis, gingival fistulae, antral empyema, blind abscess at the root of a tooth,* or *dental sepsis* (either *septicemia,* or, more often, *metastatic infections,* like *arthritis, nephritis,* or *endocarditis*).

Symptoms.—In *pulpitis,* there is pain on taking cold water into the mouth; sometimes, hot or sweet fluids will elicit pain also. In vaguely localized pain, the injection of a fine stream of cool water with a syringe along the teeth so as to enter the interdental spaces, beginning with the molars, will reveal the affected tooth.

In *periodontitis,* the tooth is sensitive at first, especially on occlusion,

and feels as though it were too long. At night, it may be spontaneously painful, and there may be a feeling of pulsation and of weight in that part of the face. Hot foods cause pain; cold stimuli do not excite pain. In acute cases, there may be fever, bradycardia, and leukocytosis. On examination, there are tenderness and swelling over the root of the tooth. On tapping a dead tooth, with a loosely held handle of a probe, the tooth yields a dull, "dead" sound in contrast with the clearer sound yielded by living teeth. Dead teeth are usually a little discolored and less transparent than living teeth. There may be swelling of the regional lymph glands. If periodontitis, or a blind abscess, or an alveolar osteomyelitis be suspected, a röntgenogram, with use of the special *dental film,* placed inside the mouth during exposure, should be made. These dental röntgenograms are of the greatest value in the search for chronic foci of infection in arthritis, and in anemia.

Gingival and periodontal infections are among the commonest causes of disease in people past middle life. The physician who fails personally to inspect the gums and teeth of his patients, under good illumination, and to call skillful dental specialists to his aid in many cases, will surely fall behind in the race of medical practice!

(*c*) *Pyorrhea alveolaris and Paradental Inflammations*

Definitions.—By *pyorrhea alveolaris* is meant a disease in which there is inflammation of several structures—the gums, the peridental membrane or ligamentum circulare, and the periosteum and the alveolar process of the jaw; it is therefore a combined gingivitis, paradentitis, and osteitis; the inflammation may cause destruction as high as the apex of the tooth, and ultimately the tooth falls out. By *paradental inflammation* is meant an acute inflammation of the periodontium and its neighborhood, not due to extension from the interior of the tooth or the apex of the root-canal, but arising in a gingival pocket.

Etiology.—If tartar collect on the teeth at the gum-margin, inflammation of the gum (gingivitis marginalis) develops. As the tartar descends, or ascends, into the alveolar socket, there is gradual atrophy of the gum and alveolus, and, later, the teeth will become loose and fall out. This process is often associated with infection and suppuration (pyorrhea alveolaris; Riggs' disease, a very serious and an extremely common disease). The Entameba buccalis, spirochetes, and bacteria can be found in the pus.

Symptoms.—The breath is foul, the odor sickening and distinctive (easily tested by passing the edge of a sheet of paper high up between the teeth and then smelling it).

There is usually more or less retraction of the gum around the neck of the tooth (collum dentis), and the gum becomes separated from the

tooth with the formation of a so-called "pyorrhea pocket," whence pus may exude spontaneously or when pressure is applied to the gums. Sometimes, a small fistula, some distance from the edge of the gum, discharges pus. As absorption proceeds and granulation tissue forms, the tooth loosens. The disease may go on for years without causing any pain. The loss of teeth is usually slow; but in some cases, this may go on rapidly, the teeth becoming very loose in a few weeks or months. Pyorrhea most often involves first the dentes incisivi, especially those of the lower jaw.

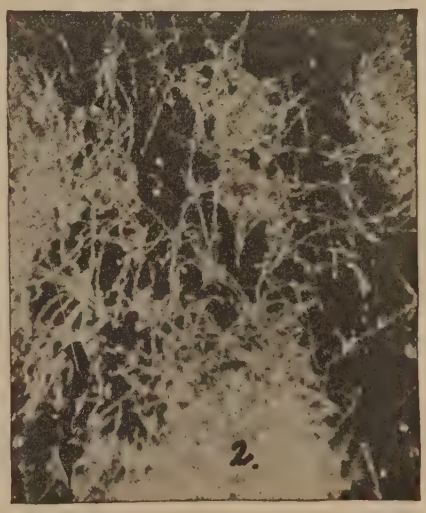

Fig. 392.—Treponema mucosum from Pure Cultures Ten Days Old, Obtained from a Case of Pyorrhea alveolaris. (After H. Noguchi, "Studies of the Rockefeller Institute for Med. Res.," Reprinted from J. Exp. Med.)

Diagnosis.—Inspection, palpation, and the paper test for the characteristic odor usually settle the diagnosis. The *Entameba buccalis* should be sought microscopically. In incipient cases, a skillful dentist may discover "pyorrhea pockets" at a stage when they might be overlooked by the physician. Pyorrhea alveolaris must be differentiated (1) from scorbutic and other forms of "spongy" gums, and (2) from simple atrophia alveolaris praecox (retraction of gums without any signs of inflammation).

I have seen many evidences of constitutional injury from such oral sepsis, and William Hunter of London has emphasized its relation to severe anemias. I recall a remarkable case of sapremia from a most extensive pyorrhea alveolaris, causing fever, extreme cachexia and marked enlargement of the liver; recovery was prompt after removal of all the teeth; the liver returned to its normal size. It is matter of every day practice to see patients with chronic arthritis, secondary to pyorrhea alveolaris or to abscesses at the roots of the teeth. Serious disorders of gastric digestion may follow the swallowing of pus from alveolar pyorrhea.

Gouty and diabetic patients are very prone to pyorrhea; but the condition occurs to a greater or less degree in nearly every one past middle life, unless the most careful prophylactic measures are maintained.

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4. Diseases of the Salivary Glands

(*a*) *Parotitis*

Etiology.—Inflammation of the parotid gland may be a *secondary* process in severe diseases (typhoid; pyemia), due to an ascending infection of Steno's duct, or it may be *primary* in epidemics (mumps; parotitis epidemica). Mumps has been described in the Section on Infectious Diseases.

Symptoms.—The situation of the swelling in front of and below the ear is characteristic. If it be hot and tender, the swelling is due to inflammation. In a child, with fever, the swelling soon becoming bilateral, the diagnosis of mumps is easily made; the face assumes a silly appearance, a strange froglike expression due to the pear-shaped face.

A unilateral parotitis, in the course of typhoid fever, or of a septic infection, often leads to an abscess of the parotid, requiring incision. An acute swelling of the parotid, without fever, disappearing, but recurring frequently, is a sign of stone in Steno's duct.

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(*b*) *Mixed Parotid Tumor*

The mixed tumors of the parotid are very characteristic growths; a failure in diagnosis will scarcely be made. A movable, irregular, nodular tumor in the region of the parotid is probably a *mixed tumor* of the parotid. The important point to decide is whether or not it is still benign. Free mobility, absence of facial paralysis and of radiating pains, speaks for benignancy—the contrary for malignancy. Pure *teratomata* also occur in this neighborhood, but are uncommon. As soon as a tumor has become malignant here, it becomes adherent to its surroundings and is particularly prone to involve the nerves of the neighborhood. A tumor, long benign, may finally undergo carcinomatous or sarcomatous change.

In the differential diagnosis of mixed parotid tumor, it should be remembered that *tuberculosis of the small lymph glands within the parotid gland* may simulate the disease. If other glands of the neck are tuberculous, the nature of the tuberculous parotid may be suspected. More rarely, there is *tuberculosis of the gland tissue of the parotid*, itself, rather than of lymph glands within the parotid capsule; cold abscess may result in either case.

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(*c*) *Salivary Ranulae and Salivary Calculi*

Ranulae.—A unilateral swelling beneath the tongue, presenting a bluish appearance through the mucous membrane, and found, on palpation, to be soft, elastic or fluctuating, is a salivary ranula. In most cases, it is a retention cyst of the duct of the sublingual gland. Rarely, dermoid cysts, lymphangiomata, or lipomata, may occur in this situation and simulate ranulae; if there be doubt, exploratory puncture is advisable.

Calculi.—A calculus may be situated in Wharton's duct, which leads from the

submaxillary gland. It may be the cause of a submaxillary ranula, or, if infected, can give rise to an acute adenitis of the gland, which then becomes swollen and painful. If a calculus be present, recurring adenitis of the submaxillary gland is common. The stone can be palpated from the mouth, and its shadow can be seen in a röntgenogram.

A similar salivary calculus in Steno's duct can give rise to corresponding complications in the parotid gland.

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(*d*) *Mikulicz's Disease*

Definition.—A symmetrical, chronic inflammation of all the salivary glands, together with the lacrimal glands. Sometimes the salivary glands alone are involved.

Varieties.—The disease may be associated with changes in the blood (leukemia; anemia). Most cases, however, are not accompanied by blood changes, though, in these, there may or may not be enlargement of the lymph glands and of the spleen (von Brunn).

The histology has been carefully studied by Hase, who describes three groups: (1) with hyperplasia of normal lymphatic tissue; (2) with chronic tuberculous granulation tissue without caseation; and (3) with tuberculous granulation tissue with demonstrable tubercle bacilli, or positive tuberculin reaction.

Tileston reserves the term Mikulicz's disease for cases of chronic, painless, bilateral enlargement of the salivary and lacrimal glands, in which we can positively exclude leukemia and pseudoleukemia.

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B. Special Diagnosis of Diseases of the Palate, Tonsils, and Pharynx

1. Inflammations of the Throat

(Sore Throat; Angina)

Inflammation of the soft palate and tonsils in the region of the isthmus of the fauces is called **angina.** If it be limited to the tonsils alone it is called **tonsillitis** (*angina tonsillaris*), if to the pharynx alone, **pharyngitis.**

(a) *Acute Catarrhal Sore Throat*

(Tonsillitis and Pharyngitis)

Symptoms.—Fever; headache; anorexia; pain on swallowing. Tonsils soft; palate and posterior wall of pharynx reddened and swollen. Mucopurulent exudate; often herpes labialis; slight enlargement of lymph glands at angle of jaw. If the crypts of the tonsils become plugged, we speak of a *lacunar tonsillitis.* If the lymph nodules themselves are inflamed, it is a *follicular tonsillitis.* These processes are diffuse, and are very commonly due to streptococcus infections, though other bacteria may be responsible. It is very important not to mistake a diphtheritic or a luetic sore throat for a simple angina. A smear and a throat culture should be made; and, if there be any suspicion of syphilis, a Wassermann test. It should not be forgotten that adenoid vegetations (hypertrophic pharyngeal tonsil) may be the site of acute infectious processes (streptococci).

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(*b*) *Phlegmonous Sore Throat*

(*Angina phlegmonosa*)

Here, pus collects in the loose submucosa, with great swelling. Abscesses form, which break of themselves, or must be opened. Among these are included *peritonsillar abscess* (quinsy), *retrotonsillar abscess,* and *retropharyngeal abscess,* with fluctuation on the posterior wall of the pharynx. In sucklings, retropharyngeal abscess is due to suppuration of retropharyngeal lymph glands; in later life, it is often secondary to osteomyelitis, or to caries, of the cervical spine.

A unilateral angina should make one think of the possibility of a tonsillar or a retrotonsillar abscess. An acute swelling of the posterior or lateral wall of the pharynx is the clew to retropharyngeal abscess.

(*c*) *Croupous, or Pseudomembranous Sore Throat*

(*Angina crouposa; Angina pseudomembranacea*)

Definition.—A violent inflammation, with formation of a false membrane (fibrinous exudate; necrotic epithelium) in the throat. The superficial form is called a "croupous," the deeper form, a "diphtheritic" inflammation.

Etiology.—Such anginas may be due to true diphtheria (Klebs-Löffler bacilli), or to streptococci (in scarlet fever, and in severe streptococcus epidemics).

During the past few years, in America, severe epidemics have been reported (Boston, Baltimore, Chicago) due to a streptococcus causing violent angina, bubolike enlargement of the cervical glands, and not infrequently septicemia and metastatic peritonitis. (See Part IV, Streptococcus Infections and Diphtheria.)

Plaut-Vincent's Angina

This is a form of necrotic angina in which grayish white necroses, with red margins, are visible on the tonsils; the necrosis is followed by sloughing and ulcer formation; the general condition is not, as a rule, much affected. It is believed to be due to a mixed infection (fusiform bacilli and spirochetae).

Note! In all anginas, careful bacteriological examination should be promptly made (smears, cultures on coagulated blood serum). A delay in

the recognition of an infection due to *Bacillus diphtheriae* is exceedingly dangerous.

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(*d*) Chronic Tonsillar Infections

These are often overlooked. The pharyngeal tonsils may be small, adherent, or buried. The glands at the angle of the jaw are usually enlarged. The condition is often first suspected owing to the coexistence of metastatic arthritis, endocarditis, or nephritis. Small abscesses are frequently found when such tonsils are excised. Such primary foci of infection should be carefully sought for in all cases of chronic invalidism. In children, infection of the pharyngeal tonsil, **infected adenoids,** should be suspected in febrile affections, otherwise unexplained. The little patients are often mouth breathers, and, usually, a chain of enlarged lymph glands is palpable in the back of the neck on one or both sides. Such children are subject to recurring otitis media.

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[Note.—See also references under Examination of the Pharynx and Tonsils and under Acute Catarrhal Sore Throat.]

(e) *Ulcer of the Throat or Tonsil*

An ulcer in this region always necessitates careful investigation as to its cause. It may be luetic, tuberculous, or cancerous.

If the regional lymph glands are not enlarged, it is probably not a luetic chancre (unless the lues be *very* recent); it may be a gumma, a carcinomatous ulcer or a tuberculous ulcer. Of these, *carcinoma* is the most common, especially in people past middle life, and, particularly, if they are addicted to alcoholism (de Quervain). A single ulcer favors the diagnosis of cancer; gummatous and tuberculous ulcers are often multiple. Pains radiating into the ear, preventing sleep, speak strongly against gumma and tuberculosis.

About a *tuberculous ulcer,* one can often see minute nodules on a red base; in *gumma,* it is common to see several round nodules undergo partial coalescence, the area then breaking down in the center. The anamnesis, the general state of the patient, the Wassermann test, and tuberculin reactions will help in diagnosis. When in doubt, a piece of the ulcer, at its margin, should be excised for histological and bacteriological diagnosis.

If the ulcer be accompanied by enlargement of the regional lymph glands, much will depend upon the time of enlargement. Has this occurred shortly before the appearance of the ulcer, and has it developed rapidly, it is probable that the ulcer is the initial lesion of syphilis (Hunterian chancre). But if the glands have not enlarged until some time after the ulcer appeared, the ulcer is either carcinomatous or tuberculous. The ulcers in Plaut-Vincent's angina have more than once been mistaken for luetic ulcers. The *treponema pallidum* is usually demonstrable in serum from luetic lesions by the Chinese ink method of Burri, or the colloidal-silver method of Nitsche.

C. Special Diagnosis of Diseases of the Esophagus

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1. Esophageal Varices

Definition.—A pathological dilatation of esophageal veins, usually due to the development of a collateral circulation after obstruction to the vena porta (cirrhosis hepatis), or to the vena cava superior. The veins may be enlarged to the size of a lead-pencil, and on rupture give rise to severe, or fatal, hemorrhage It is usually the veins of the lower esophagus that are involved.

Symptoms.—There are none until hemorrhage occurs, due to rupture of a vein during exertion, during the passage of a sound or tube, or on ulcer-formation.

Diagnosis.—Rarely made before hemorrhage occurs, unless accidentally discovered on esophagoscopy undertaken for other reasons. Hemorrhage from esophageal varix has to be differentiated (1) from hemorrhage due to gastric ulcer, (2) from hemorrhage from aortic aneurism, and (3) from that due to esophageal carcinoma. In outspoken cirrhosis of the liver, no examination of the esophagus or stomach should be made that will cause rupture of an esophageal varix.

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2. Esophagitis

Definition.—An inflammation of the wall of the esophagus.

Etiology.—*Acute catarrhal esophagitis* is due (1) to mechanical, chemical or thermal stimuli or (2) to infection (in typhoid, measles or scarlet fever). *Chronic catarrhal esophagitis* occurs most often in smokers, and in drinkers, though it may occur independently of tabagism or alcoholism in chronic passive congestion. *Acute corrosive esophagitis* is due to the swallowing of corrosive poisons, either unintentionally, or with suicidal intent; among these poisons, lye, KOH, NaOH, H_2SO_4, HCl, HNO_3, carbolic acid, sublimate, and silver nitrate may be mentioned. In *croupous esophagitis,* the cause is to be sought in (1) a direct extension from a croupous pharyngitis or (2) a hematogenous localization of some general disease. In *purulent esophagitis,* a pyogenic infection follows some injury of the mucosa, or is propagated to the esophagus through its wall from without; a circumscribed abscess may develop, or a diffuse phlegmon may extend along the greater portion of the esophagus.

Specific inflammations of the esophagus also occur (diphtheria, tuberculosis, lues, glanders, actinomycosis), but they are rare.

Symptoms.—There is pain on swallowing, localized behind the sternum. The patient says he feels as though food stuck on the way down. Much mucus is secreted in the catarrhal form; on attempting to swallow food, there is vomiting. In corrosive esophagitis, there is necrosis with sloughing. Mild cases recover; but after severe corrosion with extensive necrosis, stricture (stenosis) from scar formation follows, with dilatation and hypertrophy of the wall of the esophagus above it.

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3. Esophageal Ulcers

An ulcer here may be due (1) in inanition to pressure of the cricoid cartilage on the esophagus, or to pressure from a struma, an aneurism, or

a neoplasm; (2) in regurgitation of the stomach juice, to esophagomalacia or peptic ulcer; or (3) in esophageal varix to abrasion over the varix with formation of a "varicose ulcer."

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4. Esophageal Stenoses or Strictures

Definition.—A pathological narrowing of the lumen of the esophagus.

Etiology.—The cause (1) may lie in the esophagus itself (*carcinoma, scar-stricture, stenosing diverticulum, esophagismus*), or (2) it may be a pressure from without (*aortic aneurism, enlarged bronchial glands, mediastinal sarcoma, spondylitic abscess*).

Diagnosis.—We remember (1) that carcinoma is responsible for about three-fourths of all the stenoses; (2) that next in frequency is stricture from corrosion, and that a patient having a stricture, due to a scar, will probably give a history of corrosive poisoning (acids, alkalies). Aneurism must always be kept in mind as a possible cause, and should be ruled out by röntgenoscopy of the chest before the esophagus is sounded. For localizing the site of a stenosis, see Methods of Examining the Esophagus.

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5. Esophageal Dilatations

Varieties.—Dilatations of the esophagus may be either (a) *diffuse,* involving the whole circumference, or (b) *circumscribed,* involving only a part of the circumference (known as diverticula).

(*a*) *Diffuse Esophageal Dilatations*

These may involve the whole length of the tube, or only a part of it. There is generally hypertrophy of the muscular wall, especially in *diffuse stasis-ectasia,* above a stricture.

Fig. 393.—Dilatation of Esophagus from Cardiospasm in One of the Author's Cases. (By courtesy of X-ray Department of Prof. von Noorden's Clinic.)

An important form of diffuse dilatation is the so-called **idiopathic dilatation of the esophagus,** in which the tube, throughout its lower part only, undergoes spindle-shaped dilatation. Kinnicutt presented a remarkable specimen to the Association of American Physicians in 1904. Such a dilatation may be due to functional cardiospasm (*spastic form*), or to atony of esophageal muscles (*paralytic form*). According to F. Kraus,

idiopathic dilatation is due to a disorder of the vagus nerves causing, simultaneously, loss of the inhibitory mechanism of the cardia and atony of the esophageal musculature.

The patients complain of trouble in swallowing and of regurgitating fresh, or decomposed, foods, in large amounts. Fluids are more difficult to swallow than solids, though patients learn various maneuvers that help them to swallow for a time. Finally, they vomit, or rather the ingesta "run out" of them. They emaciate, despite a good appetite. The saliva is increased; the bowels are constipated. Sleep is interfered with by the "vomiting." Spontaneous remissions are common.

An esophageal bougie may pass easily, though, if cardiospasm exist, the stomach tube may be "pinched" as it passes through the cardiac orifice. Recognition is easy by bismuth x-ray examination (Fig. 393), though whether an organic stenosis exists at the cardia or not must be determined by the sound or by the esophagoscope.

In some of these cases, achylia gastrica is reported after a test breakfast has been given, owing to the fact that the stomach tube has not passed through the cardiac orifice, but has coiled up in the dilated esophagus!

(*b*) *Circumscribed Dilatations of the Esophagus* (*Diverticula*)

We distinguish *pressure-*, or *pulsion-, diverticula*, due to pressure from within, from *traction-diverticula*, due to a pull upon the wall from without.

Of the **pressure-diverticula** there are two types, (1) the pharyngo-esophageal pressure-diverticulum of Zenker, and (2) the pressure-diverticula of the lower esophagus. The most common is the first, of *pharyngo-*

Fig. 394.—Röntgenogram of Esophageal Diverticulum. (After C. H. Mayo, Collected Papers by the Staff of St. Mary's Hospital, Mayo Clinic, published by W. B. Saunders Co., Phila.)

esophageal type behind the cricoid cartilage; the *opening lies in the posterior pharyngeal wall,* at the junction of the pharynx with the esophagus, where there is a congenital weakness of the wall (Laimer), the diverticulum descending between it and the spine. When filled with food, the sac may form a palpable tumor in the neck, which disappears on emptying it. The breath is often fetid from retention of decomposing food in the diverticulum. This condition is met with more often in men than in women, and usually in middle or advanced life. Besides stenosis phenomena, there are (1) periodic regurgitation of the contents of the sac, (2) a cervical tumor in the supraclavicular fossa in one-third of the cases, (3) cervical noises, audible at meal times, or even between meals from movements of air and fluid in the sac, and (4) the fetid odor, mentioned above. In the *pressure-diverticulum of the lower esophagus,* the cause is a propulsion. The pocket is always in the anterior, or the lateral, wall, never in the posterior wall of the esophagus. It is a malady of advanced life.

Traction-diverticula are common. Most of them lie at, or below, the bifurcation of the trachea, on the anterior or lateral wall of the esophagus, thus corresponding in situation to the lymph glands, the tuberculous or anthracotic inflammation of which leads through adhesions and cicatricial contraction to the diverticulum.

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6. Cancer of the Esophagus

Incidence.—In order of frequency among cancers of different organs, carcinoma esophagi occupies the 4th or 5th place. Between 5 and 7 per cent of all cancers found at autopsy are cancers of the esophagus. It is commoner in men than in women (7 or 8:1), and is met with most often between the 50th and the 60th year.

It is primary cancer rather than secondary that is met with here, and it is most often of the squamous epithelial type (cancroid), though adenocarcinoma and colloid cancer are sometimes found.

Site.—It is most common at some one of the several physiological narrowings of the tube, especially opposite the bifurcation of the trachea, and at the diaphragmatic narrowing, above the cardia, or at a pathological narrowing (scar, diverticulum). It metastasizes through the lymph and the blood, and spreads steadily *per continuitatem* (often involving the mediastinum, lungs, trachea, heart, etc.). Laryngoscopic examinations have revealed the frequent involvement of the left N. vagus and N. recurrens in the growth; occasionally, the left N. sympathicus is compressed.

Symptoms.—The most constant and usually the earliest symptom is a gradually developing difficulty in swallowing (dysphagia), with regurgitation, until finally even fluids cannot be swallowed. There is marked emaciation, and cachexia ultimately develops. Severe spontaneous pains in the chest, radiating to the shoulders, neck, or back, may be an early symptom. Hemorrhage is not uncommon, especially on passing a bougie or a stomach tube (*danger!*). Inflammatory processes, originating in the growth, may extend to the bronchial lymph glands. The glands above the clavicle are sometimes enlarged. Metastases in the liver and lung are common.

Diagnosis.—Every dysphagia and every intrathoracic pain require a careful investigation. Röntgenoscopy and röntgenography of the esophagus should be undertaken at once, if a suspicion of esophageal disease exist. If the x-ray examination reveal no contra-indication, an esophageal bougie may be passed, and, in suitable cases, esophagoscopy may be resorted to. (See Methods of Examination of the Esophagus.)

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7. Foreign Bodies in the Esophagus

Occurrence.—Any practitioner may be suddenly called to attend a person who has a foreign body lodged in the esophagus. In children, this is most often a *coin;* in adults, *false teeth* make up half the objects found, *fragments of bone* coming next in frequency.

Peach-stones, nuts, surgical instruments, and safety pins are more rarely met with. Occasionally, large insects (flies, wasps, bees), leeches, or worms are swallowed and lodge in the gullet.

The foreign body lodges at one of the physiological narrowings described under methods of examination of the esophagus. By far the majority lodge at the junction of the laryngeal portion of the pharynx and the cervical portion of the esophagus, i.e., at the true entrance to the esophagus. If not soon removed, pressure symptoms with necrosis and inflammation will develop. If there be danger of suffocation, one may try to grasp the body with the index and middle finger, or with long curved forceps, as a life-saving measure.

Diagnosis.—The diagnosis depends upon (1) the anamnesis, often faulty owing to the excitement of the patient and of those about him, (2) inspection, (3) palpation and (4) röntgenoscopy; occasionally the passage of a bougie or esophagoscopy is desirable.

Röntgenoscopy when it reveals a foreign body is most helpful; if nothing be seen, the presence of a foreign body is by no means excluded. Sometimes, if no shadow be seen on ordinary röntgenoscopy, a view after giving bismuth will reveal a filling-defect at the site of the foreign body, or bismuth may lodge on its surface and cast a shadow of its shape.

Round smooth objects usually pass through without injury. Sharp bodies may pass through, injuring the wall on the way; they may have to be removed through the esophagoscope. When false teeth are swallowed, no bougie or sound should be passed; in 24-48 hours esophagoscopy may be cautiously undertaken, and, often, later, esophagotomy has to be done.

D. Special Diagnosis of Diseases of the Stomach

The diseases of the stomach, or the gastropathies, include:

1. The *inflammatory gastropathies* (acute gastric catarrh; chronic gastric catarrh, often leading to achylia gastrica; gastric ulcer).

2. The *neoplastic gastropathies* (especially cancer of the stomach).

3. *Gastropathies due to disturbed motility* (motor insufficiencies, hypermotility).

4. *Anomalies in the position of the stomach* (gastroptosis).

5. The *nervous gastropathies* (sensory, motor and secretory neuroses).

6. Foreign bodies in the stomach.

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1. The Inflammatory Gastropathies

(*a*) *Acute Gastritis*

(*Gastritis acuta*)

Etiology.—Dietetic errors; imperfect mastication; acute alcoholism; intoxications and infections. In most instances we have to deal with an acute gastric catarrh; purulent and phlegmonous gastritis are rare, at least as primary diseases, though they are more often seen as processes secondary to corrosive poisoning; pyemia; round ulcer or cancer; occasionally, a true diphtheritic gastritis occurs.

Subjective Symptoms.—Pressure and fulness after eating; anorexia; sour eructations; nausea, leading the patient to induce vomiting, which he finds gives relief; slight fever. In purulent and phlegmonous gastritis, signs of sepsis soon develop.

Objective Examination.—Coated tongue; often foul breath; epigastrium tender on pressure; stomach distended with gas. After a test breakfast, diminution of HCl and pepsin; much mucus; delayed motility. Herpes labialis is common. Not infrequently, duodenitis with slight icterus complicates the picture.

Diagnosis.—The diagnosis of acute gastric catarrh is often made as a cloak for indolence, or for ignorance. It should be differentiated (1) from *acute general infections;* (2) from a *cholecystitic attack;* (3) from *acute peritonitis;* (4) from an *acute appendicitis;* (5) from *nervous gastralgia;* (6) from a *gastric crisis of tabes;* and (7) from *angina pectoris.*

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3. *Diphtheritic Gastritis*

Rösiger* (*Rudolf*).** *Ueber Diphtherie des Magens im Kindesalter. Leipzig,* ***1909, *B. Georgi, 30 p. 2 pl. 8°.*

(*b*) *Chronic Gastritis*

(*Gastritis chronica*)

Etiology.—(1) *Primary form*, due to improper treatment of the stomach itself (dietetic errors, hasty eating, faulty mastication, lack of exercise, above all, potatorium, and tabagism), (2) *secondary form*, accompanying various organic diseases (carcinoma, severe anemia, tuberculosis, renal disease, arteriosclerosis, cardiac insufficiency, portal obstruction).

The swallowing of sputum in chronic bronchitis and tuberculosis, or of the exudate from a chronic sinusitis, a chronic pharyngitis, or a pyorrhea alveolaris, may often be harmful and set up a chronic gastritis.

Pathology.—We may have either a *hypertrophic catarrh*, with swelling of mucous membrane, granulation of surface, or polyp formation, leading later to connective tissue proliferation, and, in a few cases, to general cirrhosis of stomach walls, resembling diffuse scirrhus; or an *atrophic catarrh*, with primary atrophy of the glands (*anadenia gastrica*), thinning of the mucous membrane, and, later, dilatation of the stomach.

In the hypertrophic form of chronic gastric catarrh the granular surface is known to the pathologists as *état mamelonné,* the polypoid surface as *gastritis polyposa.* The contraction of the stomach that follows proliferation of the connective tissue of the submucosa is known as *cirrhosis of the stomach,* as *leather-bottle stomach,* or as *plastic linitis of Brinton;* it might easily be mistaken for scirrhus cancer or for the contraction that follows corrosive poisoning.

Subjective Symptoms.—In many cases, there are no symptoms directly referable to the stomach; in others, vague symptoms appear (fulness and epigastric pressure); gaseous eructations very common; heartburn; sometimes nausea; water brash or pyrosis; almost never ordinary vomiting, but frequently the so-called vomitus matutinus (drunkard's vomiting), in which, in the early morning, mucus swallowed during the night from a chronic pharyngitis is brought up. Pain is rare, except sometimes at the beginning (*gastritis acida*), and in the so-called *exfoliative gastritis,* in which bits of the surface of the mucous membrane are shed. The appetite is variable, a "pasty taste" in the mouth is complained of. There may be either constipation, or a tendency to diarrhea, especially in the early morning (*gastrogenous diarrhea of anacidity*). Mental depression may be a prominent feature.

Objective Examination.—Sallow face; coated tongue; breath often fetid; stomach distended; diffusely tender. The stomach contents contain an excess of mucus; there is diminution, or absence, of HCl (*gastritis subacida*). In the early stages, there may be an excess of acid (*gastritis acida*) with undigested starch as shown by the amidulin reaction. In late stages, there may be complete *achylia gastrica* (see below); there is then hypermotility and shortened "emptying time."

Diagnosis.—*This depends upon analysis of the stomach contents after a test breakfast, and, especially, upon finding an excess of mucus* (intimately mixed with the food residues) *that has had its origin in the stomach* (See Mucus in Stomach Contents). As a rule, there is subacidity or anacidity; rarely, a superacidity is found. Simple chronic gastric catarrh should be differentiated (1) from forms of *achylia gastrica* not due to gastritis; (2) from *carcinoma ventriculi* with gastric catarrh; and (3) from *ulcus ventriculi* and *ulcus duodeni.* If the several methods of examination (chemical, röntgenological) be faithfully carried out, it should be possible to arrive at a correct diagnosis. The mikrogastria of linitis plastica is exquisitely demonstrable by x-ray methods.

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(*c*) *Achylia gastrica*

Definition.—By *achylia gastrica* is meant a condition in which stomach juice is not secreted, as shown by the absence of HCl and of ferments in the stomach contents. In the early stages, ferments may still be secreted though HCl is not (achlorhydria, combined with hypopepsia). It must be admitted, however, that the custom of using the term achylia gastrica to mean total loss of HCl secretion, independent of the behavior of pepsin formation, is growing.

Etiology.—Age is important; in people over fifty, more than 40 per cent manifest achlorhydria. Most cases of achylia are due to *organic* disease that destroys the gastric glands (chronic gastritis, carcinoma, tuberculosis, pernicious anemia, etc.). It is possible that a *functional* achylia of nervous origin (achylia gastrica simplex), without degeneration of the glands, exists, but it is rare.

Subjective Symptoms.—These are often absent, owing to satisfactory pancreatic digestion in the intestine. When symptoms are present, they are usually those of chronic gastric catarrh (*q. v.*). In some cases, diar-

rhea is troublesome. It may be obstinate and profuse, occurring especially in the early morning.

Objective Examination.—The nutrition of the patient is often good, except when diarrhea persists. The fasting stomach is empty. The stomach contents after a test breakfast show an excess of mucus, absence of free HCl, a total acidity of 4-6, due chiefly to acid salts, and an HCl deficit of 12-16. The ferments are absent, or quantitatively diminished. The motility is usually good; indeed there is often hypermotility with patent pylorus owing to loss of the closure through the pyloric reflex. This is often associated with gastrogenous diarrhea, and lientery. Bits of the mucous membrane, owing to its increased vulnerability, are often present in the stomach contents removed by aspiration.

Diagnosis.—The differential diagnosis of *benign achylia* from that in carcinoma (*achylia maligna*) was, formerly, often difficult. Good motility, absence of stagnation phenomena and of occult hemorrhages, and negative Salomon test as well as negative Wolff and Junghans' test characterize the benign form. The negative diagnosis of malign achylia due to cancer has been greatly facilitated by röntgenological studies (*q. v.*). The practitioner should remember that every patient with pernicious anemia exhibits achlorhydria.

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(*d*) *Gastric Ulcer*

(*Ulcer of the Stomach; Ulcus ventriculi*)

Occurrence.—Round ulcer of the stomach is common. There are regionary variations in frequency; the disease seems to be twice as frequent in Europe as in the United States and Canada. Some racial differ-

ences can also be made out; thus Campbell Howard found ulcer more common in negroes and in Germans than in native Americans in Baltimore.

As to *sex,* it is apparently somewhat more frequent in women than in men; and as to *age,* it is commonest in women between twenty and thirty, and in men between thirty and forty, though it may occur at any age.

Pathogenesis.—The lesion is essentially a necrosis, but the cause of this is disputed. Some assume primary circulatory disturbances with necrosis and autodigestion from superacidity. Rosenow's recent work suggests the possibility of metastatic infection with special strains of streptococci as a cause. Ulcer can be experimentally produced in animals by injection of agglutinated bacteria into the blood stream, probably by causing embolism of small vessels (Payr). It has been suggested that disharmony in autonomic innervations produces the circulatory disturbance directly, or through spasm of the muscularis mucosæ. Many regard superacidity as the cause; others look upon it as the effect of the ulcer; it seems certain that the gastric juice as secreted has a constant acidity (Bickel), but what we know clinically as superacidity is due to retention of acid in the stomach with accumulation.

Some regard a primary vulnerability of the mucous membrane as neural, others as infectious or toxic in origin. The matter is still obscure. Trauma, anemia or chlorosis, and arteriosclerosis may be factors.

A primary disturbance of motility has been postulated as the main cause, leading to insufficient protection of the stomach wall by mucus. Still others have assumed a lack of antiferments in the blood serum or in the gastric wall.

Usually only one ulcer is present (80-90 per cent of cases); but multiple ulcers may occur, indeed, more often than was formerly thought. The commonest location is on the posterior wall (42 per cent), or on the lesser curvature (35 per cent). Pyloric ulcers often lead to scar-formation and benign stenosis. Postpyloric ulcers will be discussed under the heading of duodenal ulcer. A round ulcer with hyperchlorhydria may later on become the site of cancerous growth (*ulcus carcinomatosum*).

Subjective Symptoms.—The two cardinal symptoms of ulcer of the stomach are *pain* and *hematemesis.* In addition, vomiting, eructations, nausea, heartburn and constipation may be present.

The **pain of ulcer** is often characteristic, occurring when solid food is eaten. It may occur at once, or after a couple of hours when the acidity is higher. It is often followed by nausea, and vomiting of an intensely sour chyme, with immediate relief of the pain. Bland fluids do not excite the pain. Patients despite a fairly good appetite are afraid to eat lest pain follow; it is not uncommon to see emaciation due to this cause. Characteristic pain is present in only a part of the cases; some patients have only superacidity pains (relieved by protein food or by alkali) without vomiting; others have irregular pains, independent of food-intake, and vague dyspeptic symptoms (belching, heartburn, nausea); still others are wholly devoid of subjective symptoms (clinically *latent* ulcer), applying for treatment when surprised by a sudden hematemesis, or after marked anemia has developed from prolonged occult hemorrhages.

Hematemesis is most often due to gastric ulcer, but may result from

chronic passive congestion (cardiac insufficiency), or from rupture of a miliary aneurism; it is sometimes confused with hemorrhage from esophageal varix (cirrhosis hepatis), and must always be differentiated from hemoptysis. The blood may not be vomited, but may be passed in the feces (tarry stools of manifest hemorrhage). Tarry stools may be simulated by feces colored black by bismuth or iron, or by the ingestion of large quantities of red wine or of spinach.

Objective Examination.—*Circumscribed tenderness* in the linea alba, or a little to the left of it, midway between the xiphoid and navel, is often

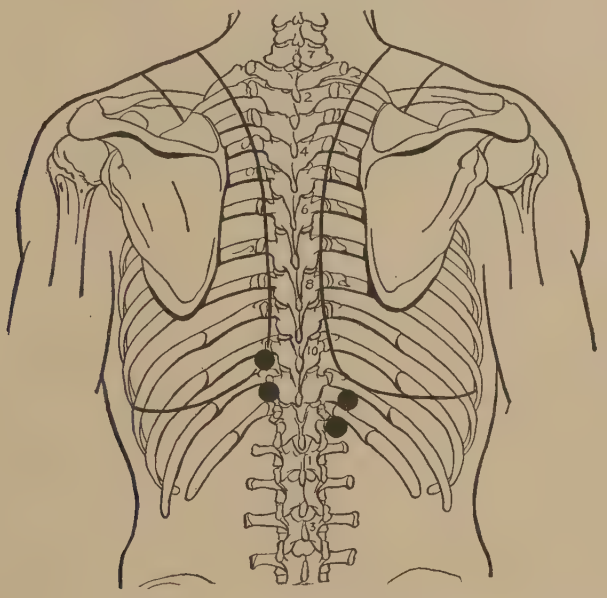

Fig. 395.—Diagram Illustrating Position of Dorsal Pressure-points in Ulcer of the Stomach.

demonstrable, but is often absent; occasionally pain can be elicited at a dorsal pressure-point, to the left of the spine near the 11th or 12th vertebral body. Hyperesthesia of the skin (Head's zone) is sometimes demonstrable.

The *examination of the stomach contents* is important. The contents of the fasting stomach often exhibit signs pointing to a disturbance of motility, even when no pyloric stenosis or hour-glass stomach exists; these signs include a slight microretention (*q. v.*) and a few yeasts and sarcinæ. So important is this finding that, in Ewald's clinic, it is regarded as imperative to make a microscopic examination of the contents of the fasting stomach in every patient suspected of ulcer. An outspoken gastrosuccorrhea may also be demonstrable in the fasting stomach.

After a test breakfast, hyperchlorhydria is usually demonstrable, though a normal acidity, or a subacidity by no means rules out ulcer.

The presence of occult blood in the stomach juice is of no diagnostic importance, but its persistence in the stool, if sources of error are ruled out, may be very helpful in diagnosis. Einhorn's thread test (*q. v.*) may help to locate the site of the ulcer.

Fig. 396.—Penetrating Ulcer of the Stomach High Up on the Lesser Curvature. Note the Flecks Representing the Crater of the Ulcer Indicated by the Arrow. The Hour-Glass Stomach is Due Partly to Spasm and Partly to Organic Changes Connected With the Ulcer. Note that the Lower Sac is Much Larger Than the Upper Sac. There is some Barium in the Bowel, Especially in the Intestinum caecum and in the Right Half of the Colon transversum. (Courtesy of Dr. Jas. T. Case.)

The very important x-ray findings in gastric ulcer have been described under röntgenology of the stomach (*q. v.*).

Diagnosis.—The anamnesis (epigastralgia, vomiting), the findings in

the stomach contents, especially from the fasting stomach, the occult blood in the stools, the results of Einhorn's thread test, together with röntgenoscopy and röntgenography, are usually decisive.

Ulcer must be differentiated (1) from *carcinoma* (especially *ulcus carcinomatosum*), (2) from *duodenal ulcer* (right-sided hunger pain, especially at 2-4 A.M.; vomiting less common; periodicity of symptoms more marked; x-rays); (3) from *gall-stones* and *cholecystitis* (absence of occult blood and of hypomotility; occasionally, urobiligenuria; character of pain; sometimes icterus; x-rays); (4) from *appendicitis* in a high appendix; (5) from *nervous epigastralgias* (absence of occult blood, and of a definite relation of pain to the ingestion of food; introduction of 100 c.c. N/10 HCl through a tube may cause no pain); (6) from *gastric crises of tabes* (pupils; knee-jerks); and (7) from *epigastric hernia* (relation of pain to exercise rather than to food; palpation). It is wise to rule out, in addition, (8) *renal stone,* (9) *intestinal parasites,* and, in women, (10) *pelvic disease.*

A therapeutic test with Leube's ulcer diet, or, better, with Lenhartz' ulcer diet, is often an aid in diagnosis in doubtful cases (See Friedenwald and Ruhräh's, Diet in Health and Disease, last edition).

Complications of Gastric Ulcer.—In addition to *hematemesis,* the most important complications are: (1) *perforation,* with general peritonitis, or subphrenic abscess, (2) *perigastritis,* with adhesions (palpable tumor; x-ray); (3) *cicatricial stenosis of the pylorus* (stasis; x-ray; visible peristalsis); (4) *hour-glass stomach* (test by distention with CO_2, or, far better, by röntgenoscopy); and (5) *ulcus carcinomatosum* (lessening of the hyperchlorhydria; gradual disappearance of sarcinæ previously present; demonstration of development of a gastric catarrh by Gluzinski's method (*q. v.*).

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(e) *Syphilitic, Tuberculous and other Specific Inflammations of the Stomach*

There is a growing literature on these comparatively rare forms of gastric inflammation.

Syphilis of the stomach is very rare in adults, though it may cause either ulcer or a gummatous infiltration. In congenital syphilis, round-celled infiltrations of the wall of the stomach, or gummatous nodules, may be found at autopsy.

Though tuberculous patients often swallow sputum containing tubercle bacilli, the acid of the stomach juice prevents, as a rule, the infection of the wall of the organ. *Tuberculous ulcer of the stomach* is, however, occasionally met with. In general miliary tuberculosis, the mucosa and the muscularis suffer. *Glanders, actinomycosis, anthrax* and *typhoid* occasionally involve the stomach.

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2. The Neoplastic Gastropathies

(*a*) *Cancer of the Stomach* (*Carcinoma ventriculi*)

Etiology.—The cause of cancer is not known. As to *age,* it is common in the stomach between 40 and 60, and is met with occasionally before 40. A family tendency is noticeable. Men are a little more often affected than women. In many instances, ulcer precedes cancer, but very often cancer occurs in persons who have never suffered from gastric symptoms but on the contrary have prided themselves on having a "sound stomach." About one-half of all cancers involve the stomach.

Fig. 397.—Stereogram of the Lesser Curvature of the Stomach, Showing Proliferation of the Tunica muscularis by an Ulcer With Carcinoma in Its Border. (After L. B. Wilson & W. C. MacCarty, Collected Papers by the Staff of St. Mary's Hospital, Mayo Clinic, published by W. B. Saunders Co., Phila.)

Site.—The pylorus, and especially the lesser curvatures, are the commonest sites; it is not rare at the cardia, but is rarer in the fundus and in the corpus ventriculi.

Subjective Symptoms.—An insidious onset is the rule, usually in people with previously healthy stomachs. The *appetite* is variable, but is usually lessened, and the patient may take a sudden dislike to meat, less often to bread or to coffee. *Pain* may be absent throughout (13 per cent, Osler and McCrae), except in cancer of the cardia, in ulcus carcinomatosum, or after perigastric adhesions have

developed. *Vomiting* is usually present, though not always an early symptom. Coffee-ground vomitus, when it occurs, is an exceedingly important symptom. If vomiting occurs soon after eating, it points to localization on the lesser curvature, near the cardia. Vomiting of large stagnant masses containing lactic acid points to motor insufficiency due to pyloric obstruction. A tendency to *constipation* is the rule, though there is *diarrhea* in 35 per cent of the cases (F. Müller).

Objective Examination.—In advanced cases, cachexia is present, with loss of weight, and the growth may become palpable, or metastases may be evident, sometimes in the skin about the navel (Osler), or in the left supraclavicular region, between the two attachments of the M. sterno-cleidomastoideus (Virchow-Troisier lymph gland). In some cases, the blood picture closely resembles that in Addisonian anemia, a real difficulty in diagnosis arising because of the achylia gastrica that accompanies ordinary "pernicious anemia." More often, there is a severe anemia of the secondary type. Occult blood (feces) if repeatedly looked for, will usually be demonstrable.

Chemical examination of the *stomach contents* reveals an absence, or at least a diminution, of free HCl, in most cases early; steadily diminishing values of HCl, pepsin and chymosin are very suspicious signs. Positive tests for lactic acid and for Oppler-Boas bacilli point to a serious disturbance of motility with stasis, usually to pyloric cancer. When large numbers of Oppler-Boas bacilli are present, they may appear in the feces ("Gram-positive stools"). Cancer in parts of the stomach other than the pylorus may cause some disturbance of motility with microretention, and increase of yeasts, bacilli and cocci (but diminution of sarcinae); flagellates may also be numerous in a slide examined on the warm stage if both HCl and lactic acid are absent. Occasionally, carcinoma particles are found, suitable for histological examination. The total chlorids may be increased, despite the deficiency of HCl (O. Reissner).

Some of the *special tests for carcinoma* may be positive. Among the more helpful are (1) that of Wolff and Junghans, (2) that of Salomon, and (3) Abderhalden's ninhydrin reaction. Very important for the early diagnosis, and especially for the comforting "negative diagnosis" is *röntgenology of the stomach* (*q. v.*). The following points may be helpful in localizing a cancer:

(a) *Cancer of Cardia* (painful deglutition, especially of solids, with regurgitation; hindrance to passage of tube or bougie; normal gastric digestion as tested by Sahli's desmoid pill; esophagoscopy; x-ray examination shows stenosis at the cardia).

(b) *Cancer of the Pylorus* (early vomiting; constipation; visible peristalsis; food residues in fasting stomach with much lactic acid; occult blood in feces; x-ray examination in stenosis shows exaggerated peristalsis, and, sometimes, antiperistalsis [Jonas]).

(c) *Cancer of Lesser and Greater Curvature, Fundus, and Body* (subjective symptoms late, or absent; progressive anemia and cachexia; palpable tumor; achylia gastrica; no stagnation; microscopic examination of cancer fragments; occult blood positive; filling defect and disturbed peristalsis on x-ray examination).

Early Diagnosis of Cancer of the Stomach.—The efforts that up to now have been made to find a reliable method are far from satisfactory. Patients with latent cancer may, unfortunately, long be free from symptoms. A palpable tumor is not necessarily non-operable, but all too often it is; and many non-palpable growths are already too advanced for removal when discovered by means other than palpation. Pyloric cancers cause disturbances of motility and stagnation early, while non-pyloric cancers are, as a rule, seen only later. Rapidly growing cancers attract attention more quickly than slow-growing tumors.

The best early tests consist of (1) examination of the contents of the fasting stomach, (2) examination of feces for occult blood, (3) Wolff and Junghans' and Salomon's tests, and, above all, (4) the newer röntgenological methods.

The *differential diagnosis* has been well summarized by C. F. Martin of Montreal. If a *tumor* exist, one must decide (1) whether it is gastric, or extragastric (duodenal, omental, peritoneal, colic, hepatic, pancreatic), and (2) if gastric, whether it is benign (foreign body, ulcer, scar, spasm, benign neoplasm) or malignant (carcinoma, sarcoma).

If *no tumor* be discoverable, there may be (1) little or no motor insufficiency (confusion possible with ulcer, simple gastric catarrh, benign achylia gastrica, or gastric neurosis); or there may be (2) motor insufficiency with definite gastrectasis (confusion possible with benign pyloric stenosis due to small scar, or to hypertrophic stenosis).

The positive, or the negative, diagnosis of gastric cancer can now be made in the majority of cases with a high degree of certainty, provided we use systematically and conscientiously the diagnostic means at our disposal. In positive cases, believed to be early, and in cases suspected to be cancer, though not demonstrably so, immediate surgical exploration should be advised.

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(*b*) *Sarcoma of the Stomach*

Primary sarcoma of the stomach is very rare, though it is occasionally met with, and then, as a rule, in young persons. Secondary (metastatic) sarcoma may involve the stomach (*e. g.,* in melanotic sarcoma).

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3. Gastropathies Due to Disturbed Mobility

(*a*) *Motor Insufficiencies of the Stomach*

Definitions.—Insufficiency of the peristolic movement of the stomach is known as *atony.* The wall of the stomach does not contract sufficiently around its contents and, through the weight of normal food, may become dilated (*atonic dilatation*).

The stomach empties its contents into the duodenum by means of its peristaltic activity (See Examination of Motility). Injury of this function is known as *motor insufficiency.* An atonic stomach is usually associated with a moderate grade also of motor insufficiency (*primary or atonic motor insufficiency*), though atony and peristaltic insufficiency may exist separate from one another. Peristole is chiefly a function of the fundus and body; peristalsis is chiefly a function of the pyloric end of the stomach.

Peristaltic insufficiency may depend upon atony (the *primary* or *atonic insufficiency* just mentioned) or upon an organic (benign, or malign) disease preventing the emptying of the stomach at the pylorus (*secondary motor insufficiency; stagnation insufficiency*). It is customary to reserve the term *dilatation* of the stomach or *gastrectasia* for the dilatations accompanying secondary motor insufficiency with stagnation.

i. Atony of the Stomach

Etiology.—Atony may be (1) a part of a constitutional defect (asthenia generalis; habitus enteroptoticus); (2) secondary to general diseases (anemia; neurasthenia); (3) due to frequent overloading of the stomach; or (4) reflex, in cholelithiasis, chronic appendicitis, etc.

Symptoms.—Clinically, atony may be symptomatically latent until the peristaltic power is also enfeebled (atonic motor insufficiency), except that

the patients say, perhaps, that they have a "weak stomach" and cannot eat fat meat, cabbage, potatoes, bran bread, etc. When motor insufficiency appears, the chief symptoms are pressure in the stomach, fullness, eructations, nausea, and vomiting, most marked about an hour after meals, and relieved by emptying the stomach. Some patients suffer from vertigo (*vertigo e stomacho læso*).

Objective Examination.—Among the findings there may be general physical inferiority; epigastric hyperesthesia; superficial epigastric splashing; increased measurements of the stomach tympany on distension with gas, with a variable degree of gastroptosis; usually superacidity; no macroscopic food residues in the fasting stomach in the morning, but some delay in emptying the stomach (motility tests; barium x-ray); and abnormal stomach filling on röntgenoscopy.

ii. Secondary Motor Insufficiency of the Stomach

(*Pyloric Stenosis with Gastrectasia*)

Etiology.—This is the result, usually, of benign, or carcinomatous, obstruction at the pylorus. A benign stenosis may be due to (1) scar of ulcer, (2) perigastritis, (3) pylorospasm, or (4) hypertrophic pyloric sphincter (most often congenital).

Subjective Symptoms.—There is vomiting at intervals (spontaneous, or artificially produced), often of food taken days before. The appetite is poor; there is marked thirst; often scanty urine owing to the gastrectasia; and constipation.

Objective Examination.—Emaciation may be pronounced and is most marked in cancer. Visible peristalsis or gastrospasm is almost pathognomonic. Increased dimensions of the stomach are demonstrable on gaseous distension, and splashing can be made out in the fasting stomach.

Food residues are demonstrable in the fasting stomach in the morning, after a test supper; free HCl may be present (benign stenosis), or absent, but lactic acid is often present (malign stenosis); H_2S is often present in benign stenosis. Occult blood in the stools is common in both benign and malign cases.

The diagnosis consists of two parts (1) the demonstration of stagnation of the stomach contents, and (2) the decision as to the nature of the primary disease causing the stagnation. Here, the history, the chemical examination of the stomach contents (fasting stomach; and after a test-breakfast), and, above all, the thorough röntgenological study of the form, size, position, and motility of the stomach are decisive.

Complications.—Tetany is common, and is due to parathyroid insufficiency, perhaps of toxic origin.

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iii. Acute and Chronic Dilatation of the Stomach and Duodenum

(*Angiomesenteric Ileus*)

Sometimes, the stomach and duodenum are simultaneously dilated, with wide-open pylorus. This may occur acutely, and was formerly described as "acute dilatation of the stomach" (Brinton; Fagge; Riedel). Conner in 1907 collected 102 cases, and Laffer, later, 207. It is not uncommon as a terminal condition in lobar pneumonia and in cardiac disease; the surgeons are familiar with it as a postoperative, or a postnarcotic complication (J. C. Bloodgood; James Bell; Codman). An arteriomesenteric incarceration, or so-called **angiomesenteric ileus,** is most often responsible.

The chronic cases of dilatation of the stomach and duodenum are commoner than is generally known. Dr. J. M. T. Finney tells me that surgeons are often surprised to find this condition when they had suspected a pyloric stenosis before operation. The obstruction is opposite the mesenteric vessels (Kundrat; Bäumler). Some years ago I suggested duodenojejunostomy to relieve this condition, as gastro-enterostomy does no good. Bloodgood, subsequently, and independently, made the same suggestion, and Stavely of Washington has performed the operation with success.

With Dr. W. L. Estes, Jr., I have described a remarkable syndrome in which *chronic dilatation of the stomach and duodenum existed in three sisters, associated with hematoporphyrinuria;* in one of them, a polyneuritis developed, and the patient suffered from tetanoid attacks.

Symptoms.—In the *acute* cases, there is distress in the epigastrium and left hypochondrium, slight distension, with dyspnea and tachycardia. The temperature may be normal. Vomiting sets in and persists; the amount may be large, the color dark brown; the odor is *not* fecal, and on chemical examination the admixture of bile and pancreatic juice may be demonstrable. A succussion splash is demonstrable. There is dullness over the distended stomach (fluid). The patients are thirsty, oliguric, and constipated. On passage of a stomach tube, a large amount of fluid may be evacuated, and lavage gives great relief to the symptoms, partly for mechanical reasons, partly, perhaps, from lessening of absorption of the toxic substances from the duodenum (See the Studies of Whipple, Stone and Bernheim). The genupectoral posture often gives great relief (release of the angiomesenteric ileus).

In the *chronic* cases of dilatation of the stomach and duodenum, there may be marked disturbances of nutrition. The condition is rarely diagnosed before surgical operation, though the diagnosis is easy on röntgenological examination ("sausage-shaped duodenum" of Holzknecht). These cases are the *bête noir* of surgeons. Hitherto, they have not known what to do for them. Gastro-enterostomy has been repeatedly done without benefit. If a thorough postural and fattening cure fail to relieve, I believe that duodenojejunostomy should be tried.

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(*b*) *Hypermotility*

Hypermotility of the stomach may occur as a symptom of duodenal ulcer, of cholecystitis, or of other irritations in the right upper quadrant. It also occurs reflexly, as a symptom in chronic appendicitis, and, sometimes, in chronic intestinal stasis. It is common, as we have seen, in achylia gastrica.

In the form of gastrospasm, it is a common symptom in vagotonic states. The methods of recognizing it have been described under Examination of the Intestines (*q. v.*). For references, see Motor Neuroses of the Stomach.

4. Anomalies in the Position of the Stomach

(*a*) *Gastroptosis*

Definition.—The low position of the stomach (exaggeration of the fish-hook type and of the drain-trap type of stomach in x-ray picture, with signs of atony) is known as *gastroptosis.* It is usually associated with enteroptosis, as a part of the general visceroptosis, in Stiller's asthenia generalis. The pylorus occupies a lower level than normal, and the main mass of the stomach is elongated. Clinically, the stomach is no longer in the epigastrium.

The recent x-ray studies of G. Forssel may make us modify our conceptions of gastroptosis. It would seem that the stomach with "deep caudal pole," or the "long stomach," may be a normal stomach as far as function is concerned.

Pyloroptosis, alone, and general gastro-enteroptosis, need not disturb function. Not every long stomach is hypotonic. When a long stomach is atonic, the x-ray shows (1) a contrast-segment at the caudal pole, (2) a saclike dilatation of the caudal stomach, and (3) a constriction above this.

According to Rovsing, two types of ptotic stomach are met with, (1) the ordinary atonic fish-hook stomach, and (2) the so-called hammock stomach. It is the latter that is most often accompanied by symptoms, especially by reflex cardiospasm.

Etiology.—The congenital factor is the most important (asthenia generalis); tight lacing and multiple pregnancies predispose. Chemical and nervous influences play a part in the production of the atony (failure of the peristolic function).

Subjective Symptoms.—Those of the accompanying general neurasthenia and gastro-intestinal atony; namely, feelings of weakness, insomnia, headache, depression, pressure and fullness in the epigastrium, nausea, eructations, anorexia, atonic constipation, and often mucous colitis.

Objective Examination.—Habitus enteroptoticus. Typical x-ray findings, mentioned above; sometimes with ileal stasis. Usually, superacidity, not always; slightly delayed motility.

Diagnosis.—The important thing to remember, is to *minimize the importance of gastroptosis* to the patient, except in the rare cases in which the accompanying gastric atony is very marked. *A great many patients and a great many physicians have had much unnecessary worry regarding gastroptosis.* If the patients are thin, it is surprising how much better they will feel after being fattened under a physician's instructions.

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[Note.—See also references on enteroptosis.]

5. The Nervous Gastropathies

(Gastric Neuroses; Nervous Dyspepsia)

Etiology.—The same causes are active as in neurasthenia and hysteria. Organic disease of other organs (appendix, gall-bladder, colon, female genitals, brain, etc.) may be accompanied by neuroses of the stomach. In tabes, especially, "gastric crises" occur.

General Characteristics.—The long duration of the symptoms is a striking feature, as is also the great variability in both the subjective symptoms and the objective findings. Often the correlation of the gastric disturbances with other nervous and psychic phenomena is easy. Nervous dyspeptics usually exhibit a lively vasomotor system. The mental state of these patients is well worthy of careful study by skilled psychiatrists.

(*a*) *Sensory Neuroses of the Stomach*

The most important are *nervous gastralgia*, and gastric hyperesthesia. The patients complain of paroxysmal attacks of pain in the epigastric region, appearing without warning, or, following upon a feeling of pressure in the epigastrium, neuralgic pains, salivation, or globus. The pain is sometimes accompanied by feelings of hunger, of nausea, or of imperative micturition. An attack may last minutes or hours. Pressure in the epigastrium often gives relief. After the attack is over, a large amount of pale urine may be passed.

The *gastric crises of tabes* are described under Tabes (See Diseases of the Nervous System).

Certain special states, including (1) *anorexia nervosa,* (2) abnormally intense hunger or *bulimia,* and (3) *nervous cardialgia,* are probably sensory neuroses.

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(b) *Motor Neuroses of the Stomach*

The principal one is *atony* of the stomach, described above. Other neuroses, belonging here, are, (1) *nervous vomiting,* (2) chewing the cud (*ruminatio humana* or *merycismus*), (3) *cardiospasm,* and (4) *pylorospasm.* Recently, x-ray studies of motility indicate that many of the spasms in the stomach depend upon reflex irritation from distant organs (appendix, colon, gall-bladder, etc.).

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(c) *Secretory Neuroses of the Stomach*

i. Nervous Anacidity (Achlorhydria), or Subacidity (Hypochlorhydria)

(Achylia gastrica nervosa)

This is met with in conditions that depress either the psyche, or the general functions of the body (incipient pulmonary tuberculosis, anemias, nephropathies, psychoneuroses). Dyspeptic symptoms are complained of; objectively, there is absence, or diminution, of HCl; the ferments are present; no great excess of mucus is found; and the variability of the chemical findings from day to day is striking.

ii. Nervous Superacidity (Hyperchlorhydria)

Etiology.—In a series of 2,000 gastric cases, Julius Friedenwald found hyperchlorhydria in 63 per cent, while in 1,592 cases of gastric neurosis, he found hyperchlorhydria in 34 per cent. When due to gastric neurosis, the commoner causes are, (1) mental overwork and fatigue, (2) gastro-intestinal atony with chronic constipation, and (3) indiscretions in the use of food, drink, coffee, and tobacco.

Symptoms.—The patients complain of pain about two to four hours after eating. It is more common after eating starchy foods than after a

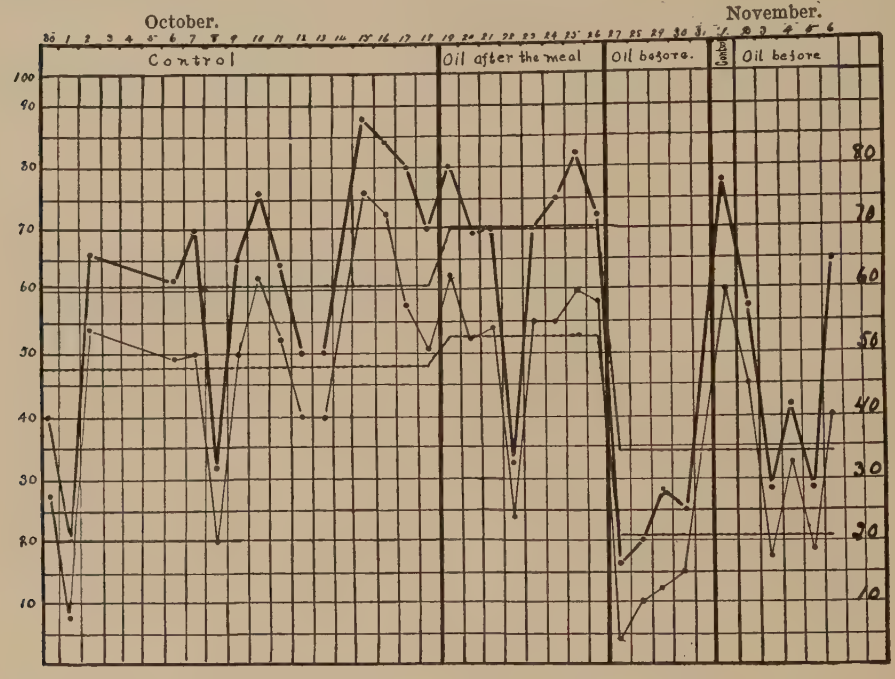

Fig. 398.—Chart Showing the Effect on the Gastric Acidity of Oil When Given Before and After Meals. Total Acidity Per Cent Indicated by the Upper (Heavier) Solid Line; Free Acidity Per Cent by the Lower Solid Line; Average Total Acidity, by the Upper Dotted Line; Average HCl, by the Lower Dotted Line. (After D. M. Cowie and J. F. Munson, Arch. Int. Med.)

meal rich in protein; and a light meal will often induce it when heavier meals are well borne. The pain is quickly relieved by the ingestion of meat, eggs or milk, or of a little sodium bicarbonate. The patients suffer from heartburn, acid eructations, and violent hunger. The appetite is good, and thirst is increased. Constipation is common; sometimes there is vomiting of acid masses that turn red congo paper blue. The motility of the stomach is usually increased, with shortening of the emptying time, though in one-third of the cases there is atony. After a test breakfast,

the HCl readings are high and starch digestion is imperfect. The tongue is clean. Phosphaturia is common; the total acidity of the urine is low; and the chlorids in the urine are diminished. Nervous hyperacidity is often paroxysmal. (*Caution!* Take care not to overlook gastric ulcer, duodenal ulcer, or reflex causes of hyperacidity such as cholelithiasis, chronic appendicitis, or ileal stasis). A condition in which the symptoms of hyperchlorhydria exist, though examinations of the stomach juice show normal values on titration of the acid, has been called "larval superacidity" (Straus); the quantity of gastric contents after a test breakfast is always large (200-350 c.c.), and the specific gravity low.

iii. Nervous Supersecretion (Gastrosuccorrhea)

The gastric juice may be secreted continuously in *Reichmann's disease* (*gastrorrhea continua chronica*), or, sometimes, only periodically (*gastrosuccorrhea continua periodica*), in increased amount. A tube passed in the early morning into the fasting stomach draws off large amounts of fluid, rich in HCl. In the periodic cases, the attacks set in with heartburn and gastralgia, and end with repeated vomiting of large amounts of greenish yellow fluid containing HCl in high concentration. During the attacks, anorexia, small pulse, scanty urine, and signs of collapse may appear. Headache is common and may be a prominent symptom, in the form of migrainelike attacks with vomiting of very acid fluids (*gastroxynsis* of Rosenbach). In such cases one should always search for signs of tabes dorsalis (pupils, knee-jerks, Wassermann test), since tabetic gastric crises are very similar.

A third form of gastric supersecretion is that in which the excessive flow is not continuous but is related to the act of digestion. Large quantities of thin fluid are found after a test breakfast, though the fasting stomach is empty (Straus, Friedenwald, Boas). This form is called *digestive gastrosuccorrhea.*

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6. Foreign Bodies in the Stomach

Foreign bodies, if present, can usually be revealed by röntgenographic examination. Thus a hair-ball or bezoar in the stomach will be visible, after swallowing barium, in the röntgenogram. Sometimes the size and number of foreign bodies swallowed may be very remarkable. I remember especially one patient operated upon by my colleague, Professor Halsted, with removal of jack-knives, many horseshoe nails, and several feet of dog chain!

a *b*

Fig. 399.—Hair-ball in Stomach: (*a*) Hair-ball Coated with Bismuth and the Upper End of It Projecting Into the Stomach-bubble; (*b*) Hair-ball Removed at Operation. (After A. Ramsbottom, Arch. of the Röntgen Ray.)

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E. Special Diagnosis of Diseases of the Intestines

The more important diseases of the intestine may be classified as follows:

I. *Inflammations of the intestine,* or, *inflammatory enteropathies,* including acute and chronic intestinal catarrh, ulcers, appendicitis, colitis and pericolitis, diverticulitis, proctitis, and certain specific inflammations of the intestine (typhoid fever, dysentery, tuberculosis, cholera, etc.).

II. *Circulatory disturbances,* or the *circulatory enteropathies,* including intestinal hemorrhage, hemorrhoids, infarction of the intestine from embolism or thrombosis of the mesenteric vessels.

III. *Enteropathies due to alterations of the lumen, or of the position,* of the intestine, including the stenoses (ileus), dilatations (diffuse and circumscribed), invaginations, axis rotations (volvulus), hernias (external and internal), and enteroptosis.

IV. *Intestinal parasitism,* or the *parasitic enteropathies,* including teniasis, ascariasis, etc.

V. *Intestinal tumors,* or the *neoplastic enteropathies,* including intestinal polyposis, cancer, etc.

VI. *Developmental errors,* or the *congenital enteropathies,* including atresia ani, atresia recti; Hirschsprung's disease (megacolon congenitum); malpositions of the intestines; and Meckel's diverticulum.

VII. The *nervous enteropathies,* including nervous diarrhea, etc.

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1. The Inflammatory Enteropathies

(a) *Acute Enteritis*

(Enteritis acuta, Cholera nostras, Acute Diarrhea, Acute Colitis)

Definition.—An acute inflammation of the intestine; the intestine may be involved as a whole; or the small or, much more often, the large intestine may be predominantly involved; or the inflammation may be localized as a duodenitis, a jejunitis, an ileitis, a colitis, a sigmoiditis, or a proctitis.

Etiology.—The *primary* form is due (1) to dietetic errors; (2) to the ingestion of indigestible or spoiled foods, or of very cold drinks; (3) to chemical irritants (drastic purgatives); (4) to mechanical irritants (scybala, calculi, foreign bodies). The *secondary* form may be due (1) to infections of various sorts (general or intestinal); or (2) to extension from adjacent inflammations.

Symptoms.—Abdominal pain or colic, rumbling, and diarrhea are the prominent symptoms. At the onset, there may or may not be fever (with or without herpes). There is a moderate leukocytosis. After many diarrheic movements, the patients feel extremely weak, and may show collapse symptoms.

If the *stomach* be simultaneously involved (gastro-intestinal catarrh), there will also be anorexia, nausea, vomiting, and a feeling of pressure in the epigastrium. When the *duodenum* participates, there is often catarrhal icterus. When the localization is marked in the *colon*, there is colic, tenesmus, and much mucus in the stools. The relation of the mucus to the food-residues helps in a decision as to its origin, and so to a diagnosis of the part of the tube involved.

If the diarrhea be profuse, the body loses much water (oliguria, thirst, cramps in the calves).

In small children, acute gastro-intestinal catarrh may be epidemic in the summer time (*cholera nostras, cholera infantum*). The little patients are seized with sudden vomiting, and violent diarrhea. The discharges are at first feculent, but soon become colorless, and sometimes assume a rice-water appearance. There is rapid loss of strength, thirst, and oliguria. In severe cases, there is collapse, with cyanosis, and cold, clammy skin (algid stage); in such patients, symptoms of cerebral anemia (somnolence, rigidity of the neck, convulsions, retraction of the eyes and fontanelles, tachycardia, and dyspnea) appear, yielding the clinical picture sometimes described as "hydrocephaloid" in children.

Diagnosis.—This is easily made from the symptoms above described and from an examination of the stools. The exact localization of the inflammatory process may be more difficult. In *duodenitis,* a slight icterus may give the clew. In *jejunitis* and *ileitis,* the mucus is present in the form of minute flocculi, intimately mixed with the fecal material, and turns green with the sublimate test owing to the presence of unchanged bilirubin; in addition, meat particles and starch granules pass through undigested, and the fermentation test for carbohydrates may be positive in sour, pultaceous stools. In *acute colitis,* the number of stools is large, there is tenderness on pressure along the colon, and mucus in larger masses (*not* bile-stained) is visible; if the mucus come from the proximal colon, it may be intimately mixed with the stool, while if it come from the distal colon, the mucus is less mixed with the fecal matter. The digestion of meat and starch may be fairly good, despite the existence of a colitis. In *sigmoiditis,* and especially in *proctitis,* there is tenesmus, with colicky pains, pollakiuria and dysuria; the mucus in the feces is on the surface and is often tinged with blood. On rectal examination in proctitis, there is spastic contracture of the sphincter, and through the proctoscope, hyperemic mucous membrane is visible.

On x-ray examination, inflamed portions of the colon may be indicated by spasticity, recognizable after a barium clyster as a narrowing of the smooth-edged shadow of the diseased portion of the bowel. Röntgenology is more helpful in the diagnosis of chronic inflammation of the intestine than acute.

In the *etiological diagnosis,* the anamnesis must be considered, and the body as a whole carefully studied. In the secondary forms, bacterial cul-

tures from the stool (*Bacillus typhosus, Bacillus paratyphosus, Bacillus dysenteriae, Bacillus enteritidis*) should be made, as well as serological tests (agglutinins). If there be any possibility of Asiatic cholera the bacteriological study of the stool by the "enrichment method" for the *spirillum cholerae asiaticae* is quickly decisive. The acute food poisoning in which the *Bacillus botulinus* has been described is known as "botulism."

We may have to rule out (1) *typhoid fever* (leukopenia, blood culture in bile-bouillon), (2) *acute appendicitis* (local tenderness and muscle spasm, increasing leukocytosis, more nausea and vomiting); (3) an *acute dysentery* (bacillary, or amebic); (4) the *diarrheal attacks of Graves's disease;* and (5) the intestinal form of *influenza.*

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(*b*) *Chronic Enteritis*

(Enteritis chronica; Chronic Enterocolitis)

Etiology.—This may follow an acute catarrh, or it may develop gradually, after a faulty diet, or after fecal accumulations in constipation; it is often the result of achylia gastrica; sometimes it follows typhoid fever, or dysentery. Chronic enteritis is common in chronic passive congestion (hepatic cirrhosis, chronic cardiac disease). It may occur as a symptom of chronic appendicitis, or of intestinal parasitism (teniasis, ascariasis, uncinariasis, etc.).

Symptoms.—The bowels are usually constipated, though often diarrhea and constipation alternate. Physical examination may reveal but little, except abdominal distention, and tenderness along the colon. The *feces contain mucus,* and sometimes undigested food residues, the latter especially when the small intestine is involved. Eventually, there may be emaciation and cachexia.

Most patients complain of a feeling of discomfort, or of slight colicky pains in the abdomen. Flatulence is a common symptom; also borborygmi. The patients feel weak, irritable and depressed.

In small children, a severe form of chronic intestinal catarrh is known as **atrophia infantum** (pedatrophy, decomposition, tabes meseraica). The child may be "reduced to a skeleton"; the skin becomes gray, wrinkled, and scaly; the eyes and fontanelles are sunken; there is marked flatulence, with enlargement of the liver and spleen; the stools are foul; and there is a tendency to complicating terminal infections (furunculosis, broncho-pneumonia, sepsis, tuberculosis); or death may occur from exhaustion or from convulsions.

Fig. 400.—Marasmus (Berliner Kinderasyl). (Photo by Dessauer, After H. Finkelstein and L. F. Meyer, in E. Feer's "Lehrb. d. Kinderheilkunde," published by G. Fischer, Jena.)

Diagnosis.—The condition may be suspected when a patient complains of abdominal discomfort, flatulence, borborygmi and irregularity of bowel action. The examination of the feces after the "detailed intestinal test diet" (*q. v.*) should be undertaken; if mucus be found, its form and distribution in the stool should be carefully observed. Röntgenoscopy may be a help in localizing the part of the bowel affected.

For the diagnosis of *diverticulitis*, see Intestinal Diverticula; and for that of *pericolitis*, see Chronic Intestinal Obstruction.

The *specific forms of enteritis, e. g.*, tuberculosis, syphilis, actinomycosis, amebic dysentery, and bacillary dysentery, are described under the infectious diseases.

In the **differential diagnosis**, we must rule out (1) *chronic amebic dysentery* (blood and mucus in the stool; *Entameba histolytica*) (See Infectious Diseases); (2) *balantidial enteritis* (anemia; *Balantidium coli*); (3) *sprue* (*q. v.*); (4) *colica mucosa* of nervous origin; (5) *tuberculous enteritis*, and (6) *syphilis of the intestine.*

A rectal examination should always be made. One will then scarcely confuse a simple proctitis with (7) a *carcinoma recti*, (8) a *luetic stricture* of the rectum; (9) an *ulcus recti;* (10) a *fissura ani;* (11) a *fistula in ano;* or (12) an *ischiorectal abscess.*

Unexplained pain in the rectum and down the thighs may be due to prostatitis, to sacro-iliac relaxation, to uterine or adnexal disease, or to a neurosis.

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(c) *Ulceration of the Intestine*

Nothnagel has subdivided the intestinal ulcerations as follows:

Group I.—Ulcers due to *necrosis:* (1) Simple duodenal ulcer; (2) Peptic ulcer of the jejunum; (3) Ulcer following burns of the skin; (4) Embolic and thrombotic ulcer (including the ulcer in polyneuritis); and (5) Amyloid ulcer.

Group II.—Ulcer due to *inflammation:* (1) Catarrhal ulcer; (2) Follicular ulcer; (3) Stercoral or decubital ulcer.

Group III.—Ulcer due to *specific acute infections:* (1) Typhoid ulcers; (2) Dysenteric ulcer; (3) Septic ulcer, etc.

Group IV.—Ulcer due to *specific chronic infections:* (1) Tuberculous ulcer; (2) Luetic ulcer, etc.

GROUP V.—Ulcer in *constitutional diseases:* (1) Scorbutic ulcer; (2) Leukemic ulcer, etc.

GROUP VI.—Ulcer in *intoxications:* (1) Uremic ulcer; (2) Mercurial ulcer.

Many of these conditions are described in other sections of this book; here, we shall consider, in particular, simple ulcer of the duodenum.

Chronic Duodenal Ulcer

Definition.—A solution of continuity, round at first, often oval later, occurring almost always in the pars superior duodeni, usually within 1 to 2 cm. of the pyloric orifice, running a protracted course, and frequently terminating fatally from hemorrhage or from perforation into the peritoneal cavity.

Etiology.—The cause is believed to be similar to that of gastric ulcer—a necrosis due to peptic digestion by acid chyme in instances where the resistance of the mucous membrane is injured through circulatory or toxic disturbance. Retention of the contents of the cap, owing to inhibition of duodenal peristalsis (secondary to ileal stasis, chronic appendicitis or cholelithiasis), may play an important part.

Duodenal ulcer is more common in men than in women. It is most frequent between 25 and 45, but may occur at any age from early childhood to advanced old age. It is more frequent than gastric ulcer; many of the cases were formerly diagnosed as gastric ulcer.

Pathology.—The chronic ulcers may be either indurated or non-indurated. The edge is often terraced; the depth of the crater varies. As a rule the ulcer presents a clean punched-out appearance, circular at first, but may later on become oval or oblong. The peritoneum over the ulcer is white and often presents the appearance of a radiating scar, easily recognizable at operation. The pyloric vein, an important landmark at operations, runs a little on the proximal side of the pylorus. If the operator recognizes it he can easily determine where the stomach ends and the duodenum begins.

Ulcer of the duodenum is most often situated on the anterior wall, equidistant from the upper and lower border, and about 1 cm. distal from the pylorus. Ulcer on the posterior surface is rare, though occasionally an ulcer there, exactly opposite one on the anterior wall, is found; such an ulcer is known as a "kissing" ulcer (Moynihan).

In the majority of cases a single ulcer exists. In about 15 per cent of the cases multiple ulcers have been found (2 to 9); these usually are of different ages.

Hemorrhage, mild or severe, is due to erosion of smaller or larger vessels. Even the aorta or the portal vein may become eroded. An extension of the inflammation through the wall may lead to periduodenitis with adhesions. Cicatrization of the ulcer may lead to stenosis of the

duodenum with secondary dilatation of the stomach. If the cicatricial process involve the region of the papilla of Vater, there may be dilatation of the stomach, with jaundice or obstruction of the pancreatic duct.

Carcinomatous change in duodenal ulcer is extremely rare, in marked contrast with gastric ulcer.

About half the fatal cases of duodenal ulcer are due to perforation of the duodenum. This occurs most often on the anterior wall, since ad-

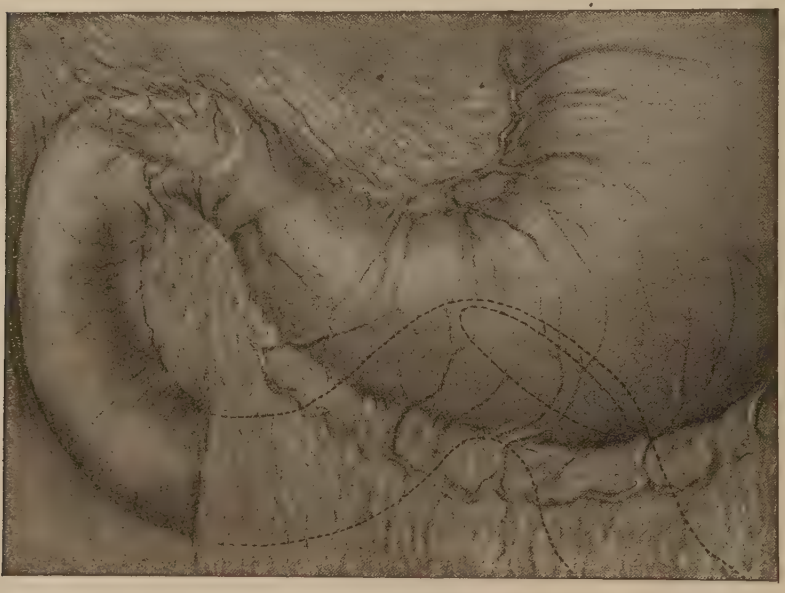

Fig. 401.—Ulcer of the Duodenum and Gastrojejunostomy After the Posterior "No-loop" Method. The Jejunum Is Applied to the Stomach as It Normally Runs to the Left and Downward. (After W. J. Mayo, "Collected Papers by the Staff of St. Mary's Hospital, Mayo Clinic," published by W. B. Saunders Co., Phila.)

hesions less often form there. If adhesions have formed before perforation, or if the perforation be minute, localized abscess, instead of general peritonitis, may result. Such abscesses may, however, undergo secondary perforation into the general peritoneal cavity, the gall-bladder, the intestine, a large blood vessel, or the thorax (through the diaphragm).

Symptomatology.—The **anamnesis** is exceedingly important, though I am not inclined to go as far as Moynihan, who maintains that it, alone, is sufficient for the making of the diagnosis.

Corresponding to the chronicity of the ulcer, there is usually a *long history* of digestive disturbances, and particularly of periodic attacks in which pain is felt from two to four hours after eating. This *pain* comes on gradually, increasing in severity. It occurs a little earlier after liquid food than after a solid meal. It usually appears when the patient begins

to feel hungry, and hence has been called "hunger-pain." At first, it is noticed only after the heaviest meal of the day; later on, it may occur after each of the three meals. The pain is relieved either by the belching of gas, or, and more especially, by the taking of food (milk, a biscuit, bread and butter). Especially characteristic is pain that wakes the patient about 2 a. m.; many patients keep food beside their beds to relieve this pain. The pain is usually in the epigastrium, a little to the right of the middle line, and may radiate to the right. Vomiting is unusual, except after duodenal stenosis has developed.

The *periodic attacks* are brought on by exposure to cold, wetting of the feet, indiscretions of diet, or by worry. These attacks are commonest during the winter months; they are almost always absent in summer. A single attack may last from two weeks to two or three months. An attack will often subside if a vacation be taken. In the interval between attacks, the patient may be entirely free from symptoms.

The patients are usually constipated; the appetite is good, though the diet may be restricted from fear of producing the pain. In late stages, the patients become emaciated and sallow, and, where there has been much oozing of blood, anemic.

On **physical examination,** there may be entire absence of signs, though, during attacks, it is not uncommon to find *tenderness* a little to the right of the middle line, an *exaggerated epigastric reflex* on the right, and some *rigidity* of the upper part of the M. rectus abdominis on the right. In *duodenal stenosis* from cicatrization, the signs are very similar to those of pyloric stenosis, though röntgenological examination shows that the site of the stenosis is below the pylorus.

Examination of the *stomach contents* after a test breakfast may reveal either an excess, or a diminution, of free HCl; in a few cases, free HCl has been absent. Blood is occasionally present in the stomach juice, but much less frequently than in gastric ulcer. Pus is absent from the stomach contents in duodenal ulcer, though present in gastric ulcer.

Intestinal *hemorrhage,* with melena, is not infrequent, but hematemesis is uncommon. *Occult blood* will nearly always be found in the stool if repeated examinations be made under proper precautions. Occult blood may sometimes be shown, also, in duodenal contents removed by Einhorn's pump. On testing for occult blood, the Schmidt-Strasburger diet should first be used, followed by a meat-free diet containing coarse vegetables (celery, radishes, etc.), to irritate the ulcerated surface and cause slight hemorrhage. The test for occult blood in the feces is more reliable than Einhorn's thread test.

The **röntgenological findings** in duodenal ulcer are sometimes very characteristic (see p. 376). Baetjer and Friedenwald emphasize the shortened emptying time of the stomach and the filling defects in the cap.

Carman (1915) lays much stress on deformity of the bulb as a diagnostic

sign of duodenal ulcer. He describes (1) the *pine-tree* or *branched-coral type* of distortion, (2) the *niche type,* varying in size from that of a wheat-grain to that of a pea, (3) the *incisura type,* single or bilateral, and (4) the *contracted-bulb type.* In addition, he values (1) *duodenal diverticula,* (2) *gastric hypertonus, hyperperistalsis and hypermotility,* (3) *six-hour gastric residue,* (4) *antral dilatation,* and (5) *gastrospasm,* as signs of ulcer of the duodenum when critically inter-

Fig. 402.—Röntgenogram of a Well-marked Case of Ulcer of the Duodenum, with Deformity of the Bulbus duodeni or Cap. Deformity Is Due to the Presence of a Large Callous Ulcer. Notice Also the Obliquely Transverse Markings of the Duodenal Contents Due to Valvulae conniventes. (Courtesy of Dr. Jas. T. Case.)

preted. With the majority of internists, Carman believes that we should not pin our faith solely to any single method of examination, but should, rather, make use of every technical method that offers help and then weigh the results as a whole.

Diagnosis.—The anamnesis (chronicity, periodicity, hunger-pain relieved by food), the absence of pus in the stomach contents, the occurrence of occult blood in the stool, and characteristic röntgenological findings—shortened emptying time of the stomach and filling-defect in the duodenal cap (See Examination of the Intestines)—are diagnostic.

We have to differentiate duodenal ulcer (1) from *gastric ulcer* (commoner in women; pain earlier after eating, in middle line and to the left; dorsal pain-point; circumscribed tenderness; vomiting and hematemesis common; pus present in gastric contents); (2) from *simple hyperchlorhydria without gastric or duodenal ulcer* (total acidity high; no pus or mucus in stomach contents; no occult blood in stool; symptoms amenable to treatment; reflex causes (cholecystitis, appendicitis) often demonstrable); (3) from *acid gastric catarrh* (mucus, but not pus, in stomach contents; hyperchlorhydria); (4) from *gall-stones and cholecystitis* (pain more severe, usually within one hour after eating and abrupt in onset, not relieved by food or bicarbonate of soda; no definite periodicity of attacks; x-ray); (5) from *chronic appendicitis with high appendix* (no occult blood in stool; absence of periodicity of attacks; absence of hunger-pain; x-ray examination).

Complications.—The three most important complications of duodenal ulcer are (1) severe hemorrhage, (2) perforation, and (3) stenosis from cicatrization.

Manifest hemorrhage is usually a late symptom. It occurs, however, in at least one-third of the cases studied. When large, it is nearly always followed by melena, though a patient may bleed to death without visible bleeding occurring in the feces. Hematemesis is exceedingly rare, though it may occur. When bleeding begins, the patient grows faint and weak, feels light-headed, looks pale, feels short of breath, and breaks out into a sweat (signs of *internal* hemorrhage). If the hemorrhage be small, but frequently repeated, a characteristic secondary, or posthemorrhagic, anemia gradually develops. In unexplained anemias, repeated examinations of the feces for occult blood should be made.

Perforation is by far the most serious complication in duodenal ulcer. It usually follows an exacerbation of the local process. At the time of perforation the patient suffers intolerable, agonizing pain; respiration is jerky; there is marked muscular rigidity in the right upper abdomen, which persists, and marked tenderness to the right of the middle line above the umbilicus. The patient does not vomit, as a rule. As the duodenal contents escape, the symptoms of acute peritonitis develop (tachycardia, abdominal distention; *tenderness throughout the whole right abdomen*, down as far as the right iliac fossa; polymorphonuclear leukocytosis; fever; constipation; Hippocratic facies; unless operation saves the patient, death in from two to five days).

The perforation of a duodenal ulcer must be differentiated (1) from *perfora-*

tion of a gastric ulcer (previous history; pain to the left of the middle line); (2) from *a perforation of the appendix* (previous history; pain less overwhelming, at first general, later localized in right iliac fossa; respiration less disturbed; Head's zone below the umbilicus); (3) from *perforation of the gall-bladder* (previous history; symptoms usually less severe); (4) from *acute hemorrhagic pancreatitis* (previous history; pain distinctly epigastric, with signs of development of "epigastric peritonitis"; marked tachycardia from the beginning; vomiting common; cyanosis; occurs most often in the obese or the pregnant; no localization in right abdomen; respiration not jerky); (5) from *acute pneumonia or pleurisy* with abdominal symptoms (temperature higher; tachypnea; less rigidity and tenderness of the abdomen; Head's zones).

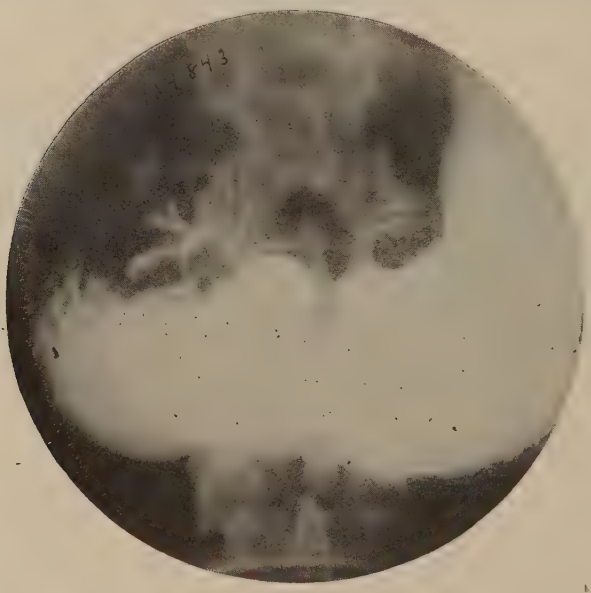

Fig. 403.—Subacute Perforating Duodenal Ulcer, Showing General Linear Deformity of the Bulbus duodeni. (By courtesy of Dr. R. D. Carman.)

In **stenosis of the duodenum**, the signs of dilatation of the stomach exist with motor insufficiency, peristaltic unrest, stagnation, and vomiting. The x-ray findings are characteristic (*q. v.*).

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[NOTE.—See also References on Gastric Ulcer, and on Examination of the Intestines.]

(*d*) *Appendicitis*

(*Inflammation of the Vermiform Process, Perityphlitis*)

Definition.—By appendicitis is meant an inflammation of the processus vermiformis or appendix, often extending to the peritoneum in its neighborhood. The condition was formerly described as perityphlitis, or inflammation of the covering of the cecum. It is now known that most inflammations in the right iliac fossa originate in the appendix, though a primary stercoral typhlitis, with extension to the peritoneum, may occur.

Site of the Vermiform Process.—Normally, the appendix lies in the right iliac fossa, its base being situated at McBurney's point, or at a point a little below this, known as Lanz's point. The position assumed by the whole appendix varies considerably (Kelly and Hurdon). In 32 per cent it lies horizontally, pointing toward the promontory of the sacrum, or laterally; in 10 per cent it lies obliquely toward the spleen; in 34 per cent it occupies an ascending position; in 24 per

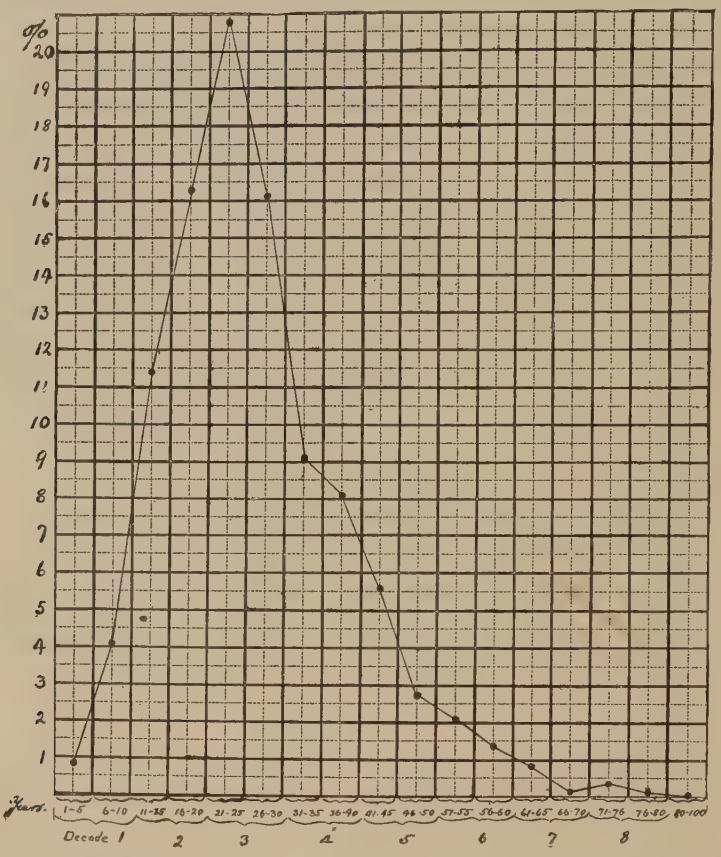

Fig. 404.—Curve Showing Incidence of Appendicitis of Various Ages, Constructed from an Analysis of 1,223 Cases Treated in the Surgical Clinic of the Johns Hopkins Hospital. Figures on the Left Indicate Percentage; Those Below, the Years of Life. (After J. W. Churchman, J. H. H. Bull.)

cent a descending position. Not infrequently, it lies posterior to the cecum and colon, in the retrocecal recess. Occasionally, it extends down into the pelvis.

The appendix is provided with a meso-appendix (*mesenteriolum processus vermiformis*), the left border of which is free and concave in outline. Its arterial supply is the *arteria appendicularis*, which is a branch of the ileocolic artery. There is a small *lymphatic gland* in the base of the meso-appendix (Clado). The orifice of the appendix in the cecum is partially guarded by a reduplication of the mucous membrane known as the *valve of the vermiform process* (Gerlach's valve). In the mucous membrane of the appendix, there is much lymphatic tissue

in the form of *aggregated nodules*, which, in early life, predispose to the localization of infections here. This adenoid tissue undergoes retrogressive change after thirty.

Etiology.—As to *age*, appendicitis occurs most often between ten and thirty, 50 per cent of the cases occurring before the twentieth year (Fitz). As to *sex*, males are attacked two or three times as often as females. *Occupation, nationality* and *heredity* do not play an important part.

Certain *local conditions* predispose to infection (kinkings, angulations, stenoses, adhesions, leading to retention). Fecal concretions and foreign bodies (pins, seeds, cherry-stones, parasites, etc.) retained within the appendix, cause local injury.

The *exciting cause* of appendicitis is bacterial infection. Any one of several organisms may be responsible, most often the *Streptococcus pyogenes* or the *Bacillus coli communis*, occasionally the *Bacillus influenzae* or the *Micrococcus lanceolatus*.

Varieties.—There is some danger in describing types of appendicitis, since, clinically, it is often impossible to differentiate between these. *It is wise to keep in mind that even a case presenting, apparently, the mildest symptoms may in reality prove to be a fatal form.* Despite our inability to distinguish always among the types that occur, clinical experience has revealed the existence of several different types, which may be roughly grouped as follows:

1. *Acute simple catarrhal appendicitis*, in which the lesions are limited to the interior of the appendix (*endo-appendicitis*). The inflammatory exudate drains into the cecum and the patient quickly recovers.

2. *Acute, diffuse, non-suppurative appendicitis*, in which there is involvement of the whole thickness of the organ, with a fibrinous exudate on its surface, but without abscess formation.

3. *Acute suppurative appendicitis with abscess formation*, either within the appendix itself, or with formation of periappendicular abscess.

4. *Acute fulminating appendicitis*, in which the pathological changes in the appendix develop with great rapidity and protective peritoneal adhesions are not formed. As a rule, acute *gangrene of the appendix*, with or without perforation, is found at operation. Sometimes fatal peritonitis develops without perforation of the appendix. A *perforative appendicitis* may occur not only in the gangrenous form, but, also, in purulent endo-appendicitis, or in acute diffuse appendicitis.

5. *Chronic Appendicitis.*—Two forms are distinguished: (1) that following an acute process, and (2) that in which the process is chronic from the start. Whether the so-called *obliterative appendicitis* is to be regarded as a chronic inflammation of the appendix, or as an involution-process in the appendix, has been much discussed. In connection with this obliterative process with fibroid change in the appendix, reflex disturbances of digestion may arise, a condition that has been described by R. T. Morris as *protective appendicitis* or *harmful involution of the appendix.*

The pathological changes found in the vermiform process as removed at operation have been carefully studied by many observers. The paper of Moschowitz, and that of MacCarty and McGrath, will be found valuable for reference. Since about half of one per cent of the appendices removed are found microscopically

to be *carcinomatous*, every obliterative appendix should be hardened and sectioned after operation. In about one-fourth of all appendices removed at operation the lumen is either partially or completely obliterated. In a considerable proportion of these, inflammatory conditions of the gall-bladder have coexisted.

Symptoms.—In most cases, the symptoms of appendicitis are so characteristic that the physician easily recognizes the condition. In a few cases, however, the onset and course are so irregular as to be very puzzling. In the **typical cases** there is pain in the abdomen, often diffuse at first, but soon becoming localized in the right iliac fossa; tenderness on palpation in the region of the appendix, rigidity of the lower part of the right M. rectus abdominis, constipation, more or less fever, sometimes nausea and vomiting, tachycardia, and leukocytosis. Often the right thigh is drawn up, and there may be an irritable bladder, especially if the appendix be in the pelvis. Rarely, there is diarrhea at the onset; it is a dangerous symptom, usually pointing to the septic gangrenous type.

In infants and in young children, the symptoms may be very misleading. Painful micturition is common, as, in the child, the appendix tends to lie in the pelvis. Deaver's advice, to regard all cases of abdominal trouble in children as appendicitis until proven to be something else, is wise.

Palpation of the appendix region should be very cautiously carried out in acute cases; in chronic cases, deeper palpation is permissible. The tenderness on pressure is usually most marked at Lanz's point, just below McBurney's point (See Examination of the Abdomen); the pain is sometimes elicitable in the left lateral position when it is not found in the recumbent posture.

After an acute attack is over, and in chronic cases, there may be no tenderness in the region of the appendix, though tenderness on pressure can then still be elicited at a point 1½ inches from the navel on the spino-umbilical line (Morris's point). This point lies over the right lumbar ganglia of the sympathetic. If it, alone, be found tender, appendiceal trouble is pointed to; if the same point be found tender on both the right and the left sides, pelvic trouble is indicated; if there be no tenderness at either the right or the left point, the trouble is situated somewhere cephalad from both pelvis and appendix (Morris).

On palpation there may be tenderness, not only on downward pressure, but also on sudden removal of the hand, permitting an *abrupt recoil* of the abdominal wall; this is believed to be a sign of peritoneal involvement (Blumberg).

In eliciting tenderness on palpation in chronic cases, *Meltzer's method* is often helpful (extension of the right knee, flexion of the right thigh, pressure at McBurney's point).

Surgeons lay a good deal of stress upon the application of the *Rovsing-Chase method* for eliciting appendiceal tenderness. Pillows are placed

Fig. 1.—Acute Appendicitis, Thirty-six Hours. The Appendix Slightly Enlarged, Tense and Injected. At the Tip a Small Gangrenous Area Surrounded by a Dark-colored Hemorrhagic Area. No Adhesions. G. P. Müller, German Hospital, Philadelphia. (After Kelly and Hurdon, "Vermiform Appendix," published by W. B. Saunders & Co., Philadelphia.)

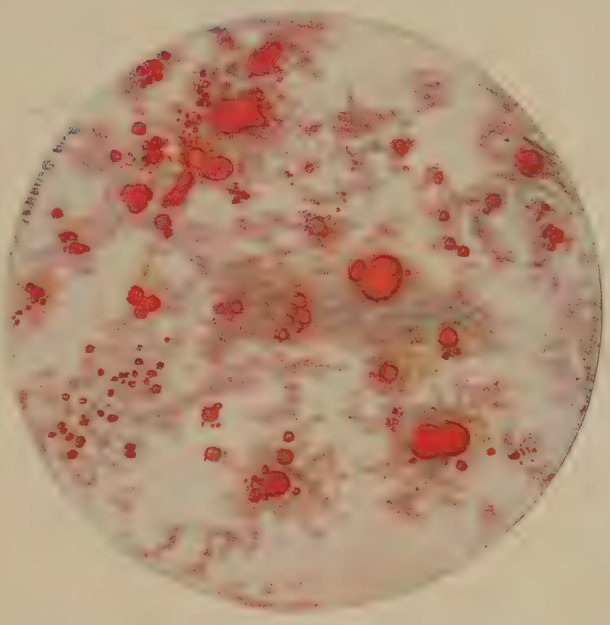

Fig. 2.—Fat in the Feces, Stained with Sudan III. (Original Drawing.)

Fig. 3.—Spirilla Plaut-Vincenti and Fusiform Bacilli. (After P. Krause, "Lehr. d. klin. Diagnostik d. inner. Krankh.," published by G. Fischer, Berlin.)

beneath the head and shoulders of the patient, and his knees are flexed. The physician, standing on the patient's left, and facing his feet, presses with the fingers of his left hand in the left iliac fossa, reinforcing the pressure with the right hand. The fingers are slowly drawn upward along the descending colon with deep pressure until the left hypochondrium is reached. This forces the gaseous contents of the colon descendens into the colon transversum and the colon ascendens. Maintaining the pressure in the left hypochondrium with the fingers of the left hand, the right hand is next placed over the transverse colon, and the fingers of this hand are quickly and forcibly depressed. This causes a gaseous wave of compression to pass across the colon transversum into the colon ascendens; arriving at the intestinum cecum, the latter is distended, and if inflammation of the cecum or of the vermiform process exist, a typical sharp pain is felt, by the patient, in the right iliac fossa.

After an attack has existed for a time, a *definite tumor* may be palpable in the region of the appendix. This may or may not be due to abscess. *A rectal examination* should always be made, and, in married women, a *vaginal examination* also, as one may thus find a tender appendix or an abscess in the pelvis.

Should the patient not be seen until *abscess* has formed, its position will depend, primarily, upon the position of the appendix, and, secondarily, upon the direction of spread of the inflammatory process.

A peri-appendiceal abscess may simulate a pelvic abscess, a psoas abscess, a perinephritic abscess, a subphrenic abscess, or an abscess in the region of the gall-bladder. In rare cases, the appendix, and the symptoms arising from appendicitis, are in the left iliac fossa, not in the right, though most instances of suspected left-sided appendicitis turn out to be diverticulitis.

The *fever* in appendicitis is rarely high (99.5-103°). Severe cases may run their course without marked fever. There is generally some *tachycardia,* but if the frequency of the pulse be greatly out of proportion to the temperature, a gangrenous process or a perforative process should be suspected.

The *examination of the blood* should not be omitted. There is nearly always a leukocytosis (10,000 to 30,000) with 80 to 95 per cent of polymorphonuclears.

Attempts have been made to construct leukocyte charts that will serve as a guide to prognosis (C. L. Gibson, Coons and Bratton, Sondern), but too much stress should not be laid upon these. A steady increase in the leukocytes, with rise in the relative percentage of polynuclears, indicates activity of the process, though not invariably gangrene (E. E. Smith). At the onset of gangrene there is sometimes a drop in the leukocyte-count.

There is usually an increased fibrin-content in the blood (*hyperinosis*). According to Smith and Bartlett, the degree of this is in direct proportion to the involvement of the peritoneum.

Two **fulminating types** have been distinguished: (1) a group in which the local pain and some of the symptoms are marked; there is rapid distention; the pulse is frequent and out of proportion to the fever; and general symptoms of peritonitis quickly follow; and (2) a far more dangerous group, in which there are no marked subjective symptoms or objective signs; the abdominal pains are general; the temperature is low, though the fever gradually increases; the pulse becomes disproportionately rapid and changes in character; there is a definite leukocytosis with high polynuclear count and hyperinosis; sometimes, though not always, toxic diarrhea is the first symptom; immediate operation is indicated.

In **chronic appendicitis,** the patients suffer from discomfort in the right iliac fossa. Slight tenderness can be elicited on pressure. There is usually obstinate constipation, and often hyperchlorhydria, though a normal acidity, or even a subacidity, of the stomach-juice may be met with. In the obliterative appendicitis, or involutional appendix, there may be no symptoms, the condition being found accidentally at operation done for other causes, but in the so-called "harmful involution of the appendix," the symptoms include headache, anorexia, chronic intestinal dyspepsia, discomfort in the region of the appendix, and tenderness at Morris's point. Sometimes a narrow, hard appendix can be palpated.

The *röntgenological study of the appendix,* in acute and in chronic cases, has already been described (see Examination of the Intestines).

Diagnosis.—When the typical clinical picture, above described, is found, even the layman makes the diagnosis nowadays, but in the atypical cases, the diagnostic acumen of the most experienced may be severely taxed. If a thorough examination be made, however, from both the clinical and the laboratory side, no serious mistakes should be made.

Perhaps the *most frequent error* is to look upon an appendicitic attack as merely an intestinal indigestion or colic, due to dietary indiscretion. The danger of treating such cases by purgatives is now, however, generally recognized. If there be any possibility of appendicitis, the patient should be kept absolutely at rest, all food should be stopped, and nothing should be given by mouth except, perhaps, a few sips of hot water; purgatives, especially, should not be given, nor should any opiate be used to relieve pain. A simple enema may be administered without danger. An ice-bag should be placed over the region of the appendix, and the general condition of the patient closely watched. If the region of the appendix be examined from time to time with reference to tenderness and muscle spasm, if the pulse and the temperature be closely followed, and if the leukocytes be frequently counted as a whole, and a differential count in stained smears made at intervals, the nature of the case should soon be revealed.

Differential Diagnosis.—Among the conditions that may simulate appendicitis may be mentioned: (1) *acute enteritis* (absence of localized tenderness or muscle spasm; diarrhea rather than constipation); (2) *acute colitis, and especially mucous colitis* (examination of feces, tender-

Fig. 405.—Röntgenogram of an Appendix Filled with Barium at the Hundredth Hour After the Barium Meal. The Colon Has Been Otherwise Emptied of the Barium Meal, But, Just Before the Röntgenogram Was Taken, Has Been Filled With a Barium Enema. (Courtesy of Dr. Jas. T. Case.)

ness along colon, x-ray examination); (3) *acute intestinal obstruction* (local meteorism followed by general distention, local symptoms, fecal vomiting); (4) *typhoid fever* (gradual onset, leukopenia, blood culture); it must not be forgotten that the appendix is sometimes involved early in typhoid fever; (5) *malaria with abdominal symptoms* (leukopenia, parasites in blood); (6) *cholecystitis* (often very difficult to differentiate if the gall-bladder be low or if the appendix be high); (7) *right renal colic* (pain extends from the back or loin along the ureter to the genitals; dysuria, hematuria, x-ray); (8) *Dietl's crises in floating kidney* (palpation of kidney, dysuria, x-ray); (9) *right pyelitis* (palpation, examination of urine); (10) *right salpingitis* or *oophoritis* (history, vaginal examination); (11) *right-sided pneumonia* or *diaphragmatic pleurisy* (general physical examination, Head's zones, Morris's point); (12) *visceral crises of the erythema group* (Osler) (history, exanthem, joint lesions).

The **diagnosis of the need of surgical exploration** is exceedingly important. It is desirable that the patient should be under close observation for the first few hours after onset, preferably in a hospital, where operation can be immediately undertaken if required. For some surgeons, there is no "medical treatment" of appendicitis, though most surgeons will admit that, in the majority of instances, a careful medical examination during the first few hours will decide whether or not appendicitis exists. If on complete rest, the withholding of food, water and medicines, and an ice-bag on the abdomen, the fever does not increase, the pulse is not disproportionately frequent, and the leukocyte count and polymorphonuclear percentage do not increase, it is better to wait until the attack is over, so that operation can be done between attacks ("interval operation"); but if there be signs of acute peritonitis when the patient is first seen, or if, after six or eight hours of observation, the symptoms continue to increase, operation should be resorted to at once. In the acute fulminating cases, above described, immediate operation is the only hope. If abscess have already formed when the patient is first seen, or if the course of the disease be protracted and abscess formation be suspected, or, again, if, after a mild onset with temporary improvement, an exacerbation occur, operation should be undertaken within twelve or sixteen hours from the onset of the attack.

Should the patient not be seen until later than this, medical treatment may be followed if the symptoms are mild, but if there are signs of a spreading inflammatory process, operation may have to be undertaken. Certainly, a non-operating physician should consult early with a surgical colleague; it is highly desirable that, in every case of suspected appendicitis, a competent surgeon should be in touch with the case from the start. The general practitioner will do well, *even in cases not requiring operation,* to associate a surgeon with him from the beginning of the attack, until

it is clear whether or not operation is necessary. In this connection, the statistics of Sahli are of interest; of 7,213 cases, 473 were operated on, 6,740 were not, and of the latter 91 per cent recovered; a recurrence occurred in 4,593 cases, of which 3,635 recovered without further recurrence.

In chronic appendicitis, operation should be performed if there is good reason to believe that the general health is being impaired from reflex disturbances of digestion.

Strong arguments in favor of surgical removal of the appendix, during or after an acute attack, are (1) the impossibility of being sure that even an attack that appears to be most mild may not become perforative and fatal; (2) the probability of recurring attacks; and (3) the danger that a severe attack may occur when the person is on a vacation in the wilds, or in some other place where operation cannot be satisfactorily performed.

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2. Circulatory Disturbances of the Intestines

Under this heading will be considered (1) Intestinal hemorrhage, (2) Hemorrhoids, (3) Embolism and thrombosis of the mesenteric arteries and veins with infarction of the bowels, and (4) Atherosclerosis of the mesenteric arteries.

(*a*) *Intestinal Hemorrhage*

(Enterorrhagia; Melena)

Definition.—By enterorrhagia is meant bleeding from the bowel; this is usually though not always followed by the appearance of black stools (melena). Melena (blood in the feces) may follow not only intestinal hemorrhage but also gastric hemorrhage and sometimes the swallowing of blood (after epistaxis, pulmonary hemorrhage or esophageal hemorrhage).

Occurrence.—True enterorrhagia occurs under many different conditions. Thus it may be met with (1) in *acute infections* (typhoid fever,

dysentery, yellow fever, malaria, sepsis); (2) in other *ulcerations* of the bowel (duodenal ulcer, jejunal ulcer, tuberculous or syphilitic ulcer); (3) in *carcinoma;* (4) in the *hemorrhagic diatheses* (purpura, scurvy, leukemias and anemias, hemophilia, icterus); (5) in *intestinal obstruction* (volvulus, intussusception, strangulated hernia after reduction); (6) in *venous stasis* (hemorrhoids, portal obstruction, obstruction to inferior vena cava; or (7) in *aneurisms;* (8) in *parasitism* (teniasis, uncinariasis, ascaridiasis, etc.).

Symptoms.—There may be *manifest hemorrhage* (bright blood when the source is low or the mobility increased; black blood, when the source is high), or *occult blood* (See Tests) in the feces. In sudden extensive hemorrhage, the patient shows the signs of internal hemorrhage (weakness, fainting, hypothermia, tachycardia, collapse, later pallor). If there be frequent small hemorrhages, the signs of secondary anemia gradually develop.

(*b*) *Hemorrhoids*

(*Rectal Piles*)

Definition.—Varicose dilatations of the hemorrhoidal plexus of veins; when in the subcutaneous tissue of the anus, or of the pars analis recti, external to the M. sphincter, they are called external hemorrhoids; when in the submucosa of the lower rectum, internal hemorrhoids.

Etiology.—Women are more often affected than men, though men are more likely early to consult a physician regarding them. The condition is one chiefly of middle life (30 to 50).

Anything that causes stasis in the hemorrhoidal veins predisposes to piles; and since the hemorrhoidal veins are drained partly by the portal system, partly by the caval system of veins, interference with the circulation in either of these systems, for example, hepatic cirrhosis in the one or myocardial insufficiency with chronic passive congestion in the other, will favor the development of hemorrhoids. Among other causes may be mentioned chronic constipation, sedentary life, obesity, pressure from organs or growths in the pelvis, pregnancy, excessive venery, gluttony, and the abuse of purgatives.

Symptoms.—When the piles are *external,* the patient has a sense of fullness at the anus, pruritus ani, and may notice blood streaks on the surface of the feces or that the toilet paper is stained with blood. Now and then, an external hemorrhoid may be drawn up into the lumen of the sphincter, become pinched, and undergo strangulation (screwlike pain, throbbing, heat). On inspection, external piles are visible as bluish-red masses, as large as a pea, a hazelnut or a walnut, often arranged in groups about the anal opening. On palpation, they are soft, unless inflamed or strangulated, when they may be firmer, due to inflammatory infiltration

or to thrombosis. When the piles are *internal,* they lie above the M. sphincter ani and are discoverable only by digital or by proctoscopic examination, though their presence may be suspected by the symptoms to which they give rise ("bleeding piles," itching, burning, tenesmus). Occasionally, internal piles may become visible externally through prolapse of the rectal mucous membrane, in which event, they often become strangulated (swelling, cyanosis, tenesmus, agonizing, screwlike pain). Some patients suffer from both internal and external hemorrhoids simultaneously.

Complications.—Inflammation from incarceration (strangulation) and infection; gangrene; sepsis; fissura ani; prolapsus recti; ulcus recti; proctitis; periproctitis; ischiorectal abscess; recurring hemorrhages; severe anemia.

Diagnosis.—Usually easy from the anamnesis, and on inspection and digital examination. Proctoscopic examination may be necessary. Women should be specifically questioned as to the occurrence of hemorrhoids since they will bear much and try all sorts of "home remedies" before referring to them voluntarily.

In the **differential diagnosis** we must distinguish hemorrhoids (1) from *carcinoma* (firm nodules, narrowing of lumen; if necessary, histological examination of excised nodule); (2) from *polypus recti* (age, common in childhood; does not bleed when punctured); (3) from *luetic condylomata* (flatter, encircle the anus, other luetic lesions, Wassermann reaction).

In the **diagnosis of complications of hemorrhoids,** in addition to inflammation and incarceration, we may recognize (1) *prolapsus recti,* from the protrusion, continuous with the skin on one side and the rectal mucosa on the other; the mass is a group of folds radiating from a central aperture; it may consist of mucosa alone (thin) or of the entire rectal wall (thick, firm); (2) *fissura ani,* from the history of severe pain on defecation and afterwards, and from inspection, a small crack or ulcer becoming visible when the patient lies on his left side and bears down, the physician opening the anal orifice with his finger and thumb; (3) *proctitis,* from the symptoms (tenesmus, throbbing and heat in the rectum, frequent micturition), from digital examination (tenderness, spasm, local heat), from the feces (mucus on the surface), and from examination with the speculum (hyperemia, hemorrhages, erosions).

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(*c*) *Embolism and Thrombosis of the Mesenteric Arteries and Veins (with Hemorrhagic Infarction or Anemic Gangrene of the Intestine)*

The symptoms produced by occlusion of the mesenteric arteries and veins are so similar that the conditions are usually considered together. Embolism of the A. mesenterica superior and thrombosis of the V. mesenterica superior occur more often than the other lesions (thrombosis of A. mesenterica superior; embolism or thrombosis of A. mesenterica inferior (rare); thrombosis of V. mesenterica inferior). Infarction due to occlusion of the A. mesenterica superior has been studied experimentally by Welch and Mall.

i. Embolism and Thrombosis of the A. mesenterica superior

Etiology.—The majority of cases are due to emboli arising from an endocarditis; a few from emboli from atherosclerotic lesions of the aorta, or other sources. Thrombosis is rare but when it occurs is due to endarteritis. Occasionally, this artery is involved in a periarteritis nodosa.

Symptoms.—This artery is more of an end-artery than the A. mesenterica inferior; it supplies the pars inferior duodeni, the jejunum, the ileum, the intestinum cecum, the colon ascendens and the colon transversum. When occluded, there is infarction of a long segment of the bowel, usually the ileum and lower jejunum; embolism of smaller branches may cause scattered infarctions with intervening healthy sections.

The symptoms following occlusion may correspond to either one of two types: (1) in the more frequent type, the prominent symptom is *intestinal hemorrhage;* the patient suffers from severe colicky pains, tenderness on

pressure and tympanites; or (2) in the less common type, *acute intestinal obstruction* is simulated (constipation, distended painful abdomen, vomiting becoming fecal).

Diagnosis.—Should symptoms of either type above described occur in a person who has endocarditis or other lesion favoring embolism, the nature of the condition may be suspected.

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(ii.) Thrombosis of the V. mesenterica superior

Etiology.—The thrombosis is often due (1) to infection at the roots of the portal system (appendicitis, dysentery, ulcus, or after laparotomy), (2) to trauma, or (3) to pressure on the portal vein (cirrhosis, neoplasm, chronic peritonitis). Infarction of the intestine follows, and peritonitis develops.

Symptoms.—These closely resemble the symptoms that follow embolism of the A. mesenterica superior (bloody diarrhea, colicky abdominal pains, meteorism).

Diagnosis.—When the symptoms appear, a study of the possible etiology may help to differentiate infarction due to venous thrombosis from that due to embolism of an artery. For references, see under Portal Thrombosis.

(*d*) *Atherosclerosis of the Mesenteric Arteries*

Vascular crises sometimes occur in atherosclerosis of the mesenteric arteries, similar to the crises known as intermittent claudication in the arteries of the lower extremities. Attacks of abdominal pain occur, often associated with gaseous distention. The condition has been called *Dyspragia angiosclerotica intermittens* by Ortner.

3. Enteropathies Due to Alterations of the Lumen, or of the Position of the Intestine

Under this heading we shall consider acute intestinal obstruction, chronic intestinal obstruction, the dilatations of the intestine, the hernias, and enteroptosis.

(a) *Acute Intestinal Obstruction*

Definition.—By acute intestinal obstruction is meant a sudden stoppage of the passage of the intestinal contents.

Etiology.—Acute obstruction may be due to a mechanical occlusion (*mechanical ileus*), or to a sudden loss of motor power of the intestinal wall (*dynamic or paralytic ileus*).

Mechanical ileus may be due to simple occlusion or to strangulation.

In **simple occlusion**, there is an obstruction to the lumen without essential injury to the intestinal wall. It may arise from:

1. *Obturation* due to abnormal intestinal contents (scybala, large gall-stones, enteroliths, masses of intestinal worms, swallowed foreign bodies). When due to a large gall-stone, the stone tends to stick in a loop of the small intestine, and sinks by gravity into the pelvis, where it can sometimes be felt on rectal or vaginal examination.
2. Intestinal *tumors*, or *scars* of ulcers.
3. *Compression* of the intestine from without (cancer of the pancreas, ovarian cyst, etc.).
4. *Spastic ileus*, which may occur spontaneously, or follow a laparotomy. It yields to atropin. Sometimes, it is unexpectedly found on operating for acute obstruction.

In **strangulation**, a portion of the intestine and its mesentery are cut off from their proper blood supply and easily undergo necrosis or gangrene. Acute strangulation is the cause in about one-third of all cases of acute obstruction. The conditions under which it arises include:

1. Incarceration of an *external hernia* (*q. v.*). Not only inguinal and femoral herniae are to be thought of, but also umbilical, obturator, lumbar, and gluteal herniae.
2. Incarceration of an *internal hernia* (in the duodenojejunal fossa of Treitz where the jejunum passes through the mesocolon transversum, in the foramen epiploicum of Winslow, in the ileo-appendicular recess, in the retrocecal recess, or, in the case of a diaphragmatic hernia, in the thorax). Diaphragmatic hernia may be suspected, if, with the signs of acute obstruction, there is marked dysphagia and a tympanitic note, or a dullness, in the region of the left lower lobe of the lung; an x-ray examination is decisive.
3. From old *adhesions*, or *bands*, after previous operations for appendicitis, cholecystitis, or ventro-fixation of the uterus. The lower ileum is most often compressed; the site is then the lower abdomen, most often in the right iliac fossa. The colon transversum may be the site (after a gall-bladder operation), or the colon sigmoideum after a gynecological operation. An angiomesenteric ileus, near the termination of the duodenum (see Dilatation of the Stomach and Duodenum), often follows laparotomy; it may occur spontaneously in emaciated scoliotic or spondylitic patients.
4. Through *axis rotation* (*volvulus*). It involves, most often, the colon sigmoideum, and follows chronic constipation, in men 30 to 60 years of age. It is rare outside of Russia, where it seems to be common.
5. Through *invagination* (*intussusception*), in which an upper portion of bowel, the "intussusceptum," extends into the part of the bowel below it known as the "intussuscipiens." It is most common in infancy and early childhood; it is sudden in onset, with pain, tenesmus, and evacuation of blood by the bowel.

Later, flatus and feces are retained. A tumor can be felt in half the cases. It may be confused with infarction of the intestine, but in the latter there is often vomiting of blood as well as passage of blood by the bowel.

Dynamic or paralytic ileus, without mechanical hindrance, may be (a) *inflammatory* in origin and occur in acute peritonitis, after trauma, and after abdominal operations, (b) *toxic* in origin, as in sepsis, typhoid, pneumonia or uremia, or (c) *reflex* in origin, as in renal or biliary colic, or in contusion, or inflammation, of the testis. One characteristic of dynamic ileus is the absence of persisting spasmodic pains.

Symptoms.—The onset is often sudden with violent pain in the abdomen, collapse and vomiting; sometimes, however, it is more gradual with colicky pains and increasing constipation. As a rule, the pain is continuous, never intermitting completely.

As a result of antiperistalsis, vomiting continues; at first it consists of gastric contents; later, it contains bile, and finally, it may become fecal. Flatus and feces cease to be passed per anum, while gas collects in the intestine oralward from the obstruction, causing meteorism, and great increase of the intra-abdominal pressure. On *inspection,* the contours of single intestinal loops may be visible as a pattern on the rather rigid abdominal wall. The breathing becomes rapid and shallow, the pulse frequent and feeble. The patients complain of thirst. The face becomes pale or slightly livid; the eyes appear sunken; the extremities are cold; and the body is bathed in a clammy sweat. On *palpation,* an area tender to pressure is found, or a mass may be felt if the obstruction be due to fecal impaction, neoplasm, or intussusception. On rectal examination, a stricture may be found or an intussusception-mass felt. On *percussion,* the distribution of tympany can be made out, as well as evidences of beginning effusion into the peritoneal cavity if these exist.

Röntgenological study should not be undertaken if acute intestinal obstruction be suspected, as there is no time to be lost; in the less urgent cases, examination after a contrast-enema is perhaps permissible, but the use of the contrast meal should not be undertaken.

In complete obstruction with strangulation, death occurs in from three to five days, while in simple occlusion the patient may live one or two weeks. Unless operation be quickly performed, cases of acute intestinal obstruction are nearly always fatal.

Diagnosis.—In investigating a case in which acute intestinal obstruction is suspected, certain important rules should be followed:

(1) No purgative should be given; (2) no opiate should be administered, as it may mask symptoms important for the diagnosis; (3) no food should be permitted; (4) thorough lavage of the stomach should be carried out promptly; (5) if careful digital examination of the rectum reveal no stricture, intussusception or other obstruction, then recurrent irrigation of the bowel should be undertaken to lessen distention; this promotes the com-

fort of the patient, and facilitates the physician's study of the case; (6) all hernial orifices should be carefully inspected and palpated for strangulated hernia, and the thorax should be examined for diaphragmatic hernia; (7) the feces obtained by lavage should be tested for blood, and the urine should be tested for indican; (8) if possible, a competent surgeon should be associated with the general practitioner from the very beginning, and consultations should continue, at frequent intervals, until a decision as to the need of operation is reached.

We seek (1) the *nature* and *cause* of the obstruction, and (2) its *site.* All the hernial orifices should be carefully examined for strangulated hernia, and a rectal examination should always be made.

An *acute* is distinguished from a *chronic* obstruction, not only by its sudden onset, but also by the completeness of the stoppage. Besides the *colicky pains* and the *abdominal pattern* of contracting bowel (seen also in chronic obstruction), vomiting is a very important, and a constant, symptom. The general condition suffers rapidly from lack of fluid intake and from absorption of toxins. Oliguria, a small, frequent pulse, and rapid and shallow breathing are other features. In the beginning, the differentiation from acute perforative peritonitis on the one hand, and from the various forms of abdominal colic (biliary colic, renal colic, gastric crises, acute pancreatitis, torsion of the pedicle of an ovarian tumor with necrosis), which may be associated with sudden shock and reflex paralysis of the wall of the bowel, on the other hand, may be difficult. Entire absence of sound on repeated auscultation over the abdomen, together with general, not circumscribed, distention, speaks for peritonitis.

Local meteorism may be helpful in diagnosis if the patient be seen early; later, the distention becomes general.

Local meteorism is absent, or confined to the epigastrium, in *duodenal stenosis;* and the abdomen is flat. The vomitus contains bile, but it is not fecal. An obstruction here may be an angiomesenteric ileus, a Treitz's hernia, or a compression from a band in tuberculous peritonitis.

In *stenosis of the small intestine below the duodenum,* the meteorism is either general, or most marked in the umbilical region. Fecal vomiting occurs, and increased peristalsis may be visible. Here an obstruction may be due to bands, volvulus, intussusception, internal hernia, tuberculosis, or neoplasm.

In *stenosis at the valvula coli,* there may be a palpable mass in the right iliac fossa, due to intussusception, volvulus, tuberculosis or carcinoma.

In *stenosis at the flexura coli dextra,* the meteorism is general; the cecum and the colon ascendens are distended; fecal vomiting occurs; on rectal injection 1½ to 2 *l.* of fluid can be introduced; and, often, a carcinomatous mass is palpable.

In *stenosis at the flexura coli sinistra,* the colon transversum is also distended; on rectal injection, 1 to 1½ *l.* of fluid can be introduced; the obstruction may be due to carcinoma, or less often to lues or to tuberculosis.

In *stenosis of the colon sigmoideum,* the meteorism is general; the cecum is markedly distended; there is very little peristalsis; on rectal injection, rarely more than ½ *l.* of fluid can be introduced; the obstruction may be due to a car-

cinoma, or to a volvulus, but is not infrequently due to a benign peridiverticulitis.

In *stenosis of the upper rectum,* the meteorism is general; there may be alternating constipation and diarrhea; sometimes there is tenesmus; digital and proctoscopic examinations are helpful; the obstruction may be due to luetic stricture, to carcinoma, or to inflammatory or neoplastic conditions in the pelvis.

In *stenosis of the ampulla recti,* there is tenesmus, fluid, or ribbon-shaped stools, and on digital or proctoscopic examination the cause will be found to be, usually, either carcinoma or syphilis.

In *volvulus,* the left lower quadrant protrudes, or there may be an S-shaped protrusion in the upper left and the right lower quadrants. Distention of the large intestine by air or water may help.

Intestinal *hemorrhage* is often met with in invagination, and, sometimes, in volvulus.

In volvulus, in intussusception, in neoplasm, and in coprostasis, a *tumor* may be demonstrable in the abdomen. In intussusception, the invaginated intestine of the infant may be palpable, usually to the right of the spine, though sometimes in the rectum; it may even protrude from the rectum (*Caution!* Do not mistake this for a neoplasm).

In *distinguishing between obstruction of the small intestine and that of the large intestine,* certain points are helpful. Thus, in the former, the pain, fecal vomiting and collapse appear earlier, and by the second or third day, indicanuria is demonstrable; while in the latter, indicanuria is absent, and a contrast-enema may be used for x-ray demonstration of the site of the obstruction. In acute obstruction, the majority of cases can, as de Quervain suggests, be divided, clinically, into three great groups: (1) an *acute obstruction arising on the basis of a chronic obstruction* (most often cancerous in the old or tuberculous in the young); (2) *an intermittent ileus,* in which sudden temporary attacks of acute obstruction occur with intervals during which symptoms are absent (most often due to (a) volvulus of the colon sigmoideum or of the ileocecal region, (b) incarceration of internal hernias, (c) angiomesenteric ileus, or (d) temporary obstructions from bands, kinks, or a Meckel's diverticulum); and (3) a *sudden obstruction without previous warnings* (in cancer, in tuberculosis, or in obturation from gall-stone).

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(*b*) *Chronic Intestinal Obstruction*

Symptoms.—The patients have (1) recurring attacks of **colicky pains** in the abdomen (not due to ordinary colica mucosa), usually referred to

the same area, and (2) signs of **dilatation** of the intestine (local meteorism, splash), and of **hypertrophy of the wall** of the bowel above the stenosis, shown by abnormal contractions visible as patterns, and palpable, through the abdominal wall; often, as a contraction lets up, a gurgling

Fig. 406.—Dilatation of the Cecum and of the Transverse Colon Due to Obstruction Below the Splenic Flexure. A Band of Adhesions About an Inch Wide Encircled the Descending Colon at + +; There Is Spasticity of the Bowel Below the Obstruction. 1. Splenic Flexure; 2. Transverse Colon; 3. Descending Colon; 4. Cecum. (X-ray Dept., J. H. H.)

murmur is audible over the stenosis. The second symptom is most often met with in stenosis of the small intestine. In chronic obstruction, unlike the acute, there is no vomiting. Constipation is an important sign if it be of recent occurrence in a person previously free from it; otherwise, it is not significant. The presence of pus and of blood in the stool indicates ulceration, but by no means necessarily cancerous. Mucus in the feces points simply to colitis, but it is present in simple colitis as well

as in tuberculosis and cancer. Loss of weight and cachexia may be important signs.

The symptoms may, for a long time, be *intermittent*, periods of colicky pain and visible contractions alternating with symptomless intervals. Not all cases are progressive. The *site of the stenosis* may be determining as regards certain of the findings. Thus a mass may be palpable in the course of the large intestine. Nowadays, the site of a stenosis in chronic obstruction can be easily found by röntgenological study (contrast enema; contrast meal).

Etiological Diagnosis.—In chronic obstruction, the stenosis may be due to either (1) a concentric narrowing, or (2) pressure from outside the bowel.

A **concentric narrowing** may be due to carcinoma, tuberculosis, lues, or scar of non-specific ulcer. Tuberculosis may occur at any age; it is

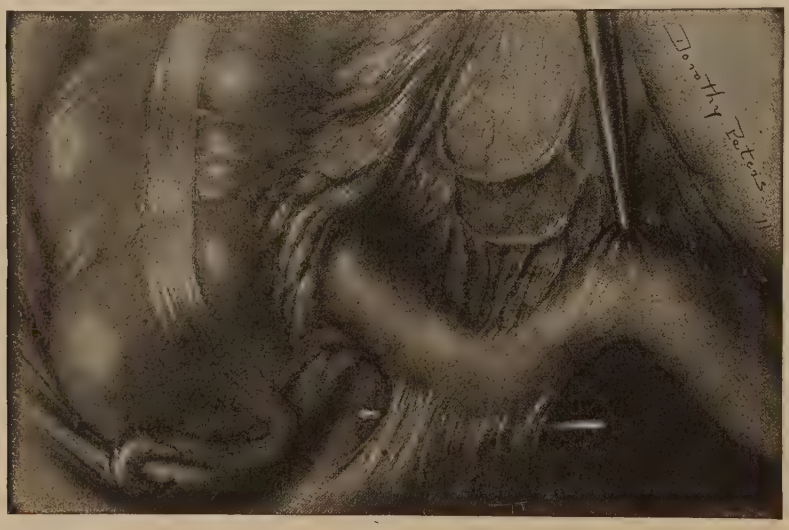

Fig. 407.—A Form of Lane's Kink with the Adhesions Causing It. (After C. H. Mayo, "Collected Papers by the Staff of St. Mary's Hospital, Mayo Clinic," published by W. B. Saunders Co., Phila.)

met with most often in the small intestine, or in the cecum. Carcinoma affects, as a rule, the large intestine; it is met with from the age of 30 on, in the rectum, sigmoid, or cecum, or at the right or left flexure of the colon. Luetic stricture, when it occurs, usually involves the rectum.

A chronic stenosis due to **pressure from without** may be due to (1) *direct compression* (retroflexed pregnant uterus; carcinoma of the uterus, ovary, or kidney; sarcoma); (2) *fixation of the bowel by adhesions or bands due to inflammation* (appendicitis; tuberculous peritonitis; perimetritis; perinephritis); or (3) *infiltration of the intestinal wall*

(pericolitis; Jackson's membrane; peridiverticulitis). In all these conditions, a röntgenological study may be of the greatest help in differential diagnosis.

The form of chronic obstruction due to a congenitally large colon is described further on (see Hirschsprung's Disease).

(c) *Dilatations of the Intestine*

Dilatations of the intestine may be diffuse or circumscribed.

Diffuse dilatation occurs (1) proximal to intestinal obstruction of various sorts, and (2) as a congenital malformation (as in Hirschsprung's disease).

Circumscribed dilatations or **diverticula** may occur in any portion of the large intestine. Meckel's diverticulum from the small intestine is a congenital anomaly (*q. v.*). Acquired diverticula are most common in the colon sigmoideum and in the colon descendens.

We shall discuss more particularly here the diffuse dilatation of the ileum, and the circumscribed dilatations or diverticula of the colon.

i. Dilatation of the Ileum, and Ileal Stasis

Definition.—In this condition, the lower part of the ileum is for a variable distance the seat of diffuse widening of the lumen (*ileal dilatation*); and there is a pathological delay of the passage of the intestinal contents through it (*ileal stasis*), this stagnation leading sometimes to pathological fermentations and the absorption of poisonous substances into the blood (*intestinal auto-intoxication,* or *alimentary toxemia*).

Etiology.—Aside from organic obstruction in the ileocecal region from cancer and from tuberculous and actinomycotic lesions, there are three principal causes of ileal dilatation and ileal stasis. These are:

1. *Adhesions in the region of the terminal ileum causing compression or kinking of the bowel* and thus obstructing its lumen; these adhesions may be the result of the regular embryological peritonitis that occurs in all mammalian embryos (A. Keith), or of a peritonitis occurring after birth; in the bibliography, much has been made of *Lane's Kink,* as a cause of ileal stasis.

2. *Spasm of the terminal four inches of the ileum,* known as the *ileocecal sphincter mechanism* (Keith, Hertz, Case); normally, this sphincter is responsible for a certain delay of the chyme in the lower ileum; in certain pathological states, especially in acute and chronic appendicitis, this ileal delay is pathologically lengthened owing to spasm of the sphincter; dilatation of the ileum proximal to the sphincter and ileal stasis result.

3. *Incompetency of the valvula coli* (or ileocecal valve); according to J. T. Case, this reflux of colonic contents into the ileum is the commonest cause of diffuse dilatation of the ileum, and of ileal stasis. Normally, the valvula coli is competent, but in about 1 out of every 6 patients presenting gastro-intestinal

symptoms examined by x-ray methods, the valvula coli has been found incompetent (Case). Incompetency may be due to congenital defect in the valve, or, more often, to colonic stasis due to bands, adhesions, etc.; most patients with incompetency are constipated.

Fig. 408.—Ileal Stasis in a Case of Incompetency of the Valvula coli and Adhesions of the Terminal Ileum. The Adhesions Indicated at (a) Are Associated with Inflammation of the Appendix. At (b) the Shape of the Ileum at the Ileocolic Junction Is Characteristic of the Disinvagination of the Ileum Seen in Cases of Marked Incompetency. This Shape of the Ileum Can Easily Be Made Out at Operation and Is Characteristic of Incompetency. (Courtesy of Dr. Jas. T. Case.)

Symptoms.—Intestinal stasis, or auto-intoxication of intestinal origin, has for a long time been held responsible for a great variety of constitutional symptoms (headache, lassitude, "biliousness," emaciation, neuras-

thenic symptoms, mental depressions), as well as for certain diseases of the eye, and certain cutaneous manifestations (see discussion on Alimentary Toxemia, Proc. of the Royal Society, London, 1913). The theory was largely developed in Paris, through the writings of Bouchard, and, later, of

Fig. 409.—Röntgenogram of an Ordinary Case of Incompetency of the Valvula coli as Tested by Contrast Enema. Still More Convincing Evidence of Incompetency of This Valve Can Be Brought by Demonstrating the Reflux of Digested Food Into the Ileum Some Hours After It Has Once Passed Through the Valvula coli Into the Colon. (Courtesy of Dr. Jas. T. Case.)

Metschnikoff. A practical surgical application was made by Arbuthnot Lane of London; convinced that continued stasis in the drainage system is exceedingly dangerous and that it is necessary to do something medically

or surgically to relieve it, he devised several surgical operations (colectomy, short circuitings, release of kinks) to cure it, and obtaining brilliant results in certain cases, soon obtained a large following. It has since turned out that most of these operations are entirely unnecessary, but as a result of the increased attention paid to the subject, we have, today, a much better knowledge than ever before of the conditions that underlie intestinal stasis, and of the means of preventing and of remedying them.

Diagnosis.—If dilatation of the ileum be suspected, the feces should be examined after an intestinal test-diet, and an x-ray examination should be made to determine, (1) *whether dilatation exists*, and (2) if found, *what the precise cause is, and the duration of the accompanying ileal stasis* (see Röntgenological Examination of the Intestine).

It is very rare that surgical operation is indicated in ileal stasis. As a rule, medical measures suffice and are better.

It is to be remembered that ileal stasis may exist without any signs of alimentary toxemia, and the symptoms supposed to be characteristic of alimentary toxemia may be present when there is no demonstrable ileal stasis. Ileal stasis does appear, however, to be more important clinically than colonic stasis.

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ii. Acquired Diverticula of the Colon

Occurrence.—While diverticula may occur in the small intestine, in the vermiform process, or in the large intestine, they are especially often found in the lower part of the colon descendens and in the colon sigmoideum, where they are usually multiple. As many as 400 diverticula have been found in a single case. They are often seen in two rows at the sides of the bowel, or close to the attachment of the mesocolon. They are most frequently in the appendices epiploicae, often appearing as a double row of symmetrically placed pockets corresponding to these appendices. They may occur, however, independently of the appendices.

These diverticula vary in size from that of a grain of wheat to that of a hazelnut, or larger. The orifice is often narrower than the maximal diameter of the diverticular sac. Usually, one sees a few scattered through the colon, then many crowded together in the colon sigmoideum, with abrupt cessation when the rectum is reached. The diverticula contain fecal matter and, sometimes, concretions. In the beginning, they are probably true diverticula; that is, all the walls of the intestine participate in their formation; later on, the muscular coat largely atrophies, as the sac enlarges.

Etiology.—*Age* is important; though diverticula may occur in young people, they are rare before the fiftieth year, and the average age of occurrence is sixty. *Males* are twice as often affected as females. Most of the patients are *obese*, or have been obese; the patients may be thin when the condition is discovered. Protracted *constipation* is probably the most important cause, increasing, as it does, the intrasigmoid pressure. The flatulence associated with the constipation also favors diverticulum formation. The diverticula occur at *weak spots in the wall* of the bowel, especially at the point of entrance and exit of the blood vessels.

Symptoms.—The diverticula of themselves do not cause symptoms; but when certain secondary pathological processes (diverticulitis and peridiverticulitis) develop in them, important symptoms may appear. In the absence of these complications, diverticula, if recognized at all, are usually found only accidentally on x-ray examination of the intestine.

Diverticulitis

Definition.—An inflammation of the walls of intestinal diverticula, especially in the colon sigmoideum.

Etiology.—The diverticula become inflamed as a result of bacterial invasion following the local action of feces under pressure, or of concretions within the diverticula. Either an acute or a chronic inflammation may develop. In *acute* inflammation, there may be (1) a simple catarrh, or (2) an acute gangrenous process may develop, with or without local abscess; in some instances there is

(3) perforation of a diverticulum, with the development of a local or of a general peritonitis. In *chronic* diverticulitis, several forms have been distinguished. The most important is (1) the chronic hyperplastic or stenosing form generally described as peridiverticulitis; other forms are (2) the chronic adhesive diverticulitis, which may cause either acute or chronic intestinal obstruction, and (3) the enterovesicofistulous diverticulitis, in which a fistula between the colon sigmoideum and the urinary bladder develops, air and feces passing out through the urethra.

Fig. 410.—Diverticulitis. The Sigmoid Has Been Laid Open Longitudinally. A Diverticulum Containing a Sloughing Ulcer Can Be Seen at the Lower Right Hand; Another Is Sectioned Near the Lateral Needle. (After W. J. Mayo, L. B. Wilson and H. Z. Giffin, "Collected Papers by the Staff of St. Mary's Hospital, Mayo Clinic," published by W. B. Saunders Co., Phila.)

Symptoms.—The clinical picture is very much like that of appendicitis, except that the trouble is in the left lower abdomen rather than in the right lower quadrant. These symptoms consist of spontaneous *pain*, *tenderness* on pressure, *rigidity* of the lower rectus, and *constipation*. Sometimes there is a palpable *tumor* in the inflamed area. Most of the cases described in the literature as left-sided appendicitis, sigmoiditis, and perisigmoiditis, are really examples of diverticulitis or peridiverticulitis of the sigmoid.

Local *abscess* frequently occurs, in which event an elongated, sausage-shaped mass can usually be felt a little above Poupart's ligament on the left, and often parallel with it; the mass is tender and not well defined. In the *perforative cases*, the signs of acute peritonitis quickly develop if the cases are not immediately operated upon.

The *chronic* cases, especially the chronic hyperplastic or stenosing form, known as *peridiverticulitis*, may closely mimic carcinoma of the sigmoid, and a wrong diagnosis is frequently made. With signs of a chronic intestinal obstruction at the level of the sigmoid, the possibility of a benign peridiverticulitis should always be kept in mind.

Diagnosis.—The occurrence of pain in the left lower quadrant of the

Fig. 411.—Röntgenogram of Multiple Diverticula of the Colon. This Was Made a Number of Days After the Colon Had Been Otherwise Emptied of the Barium Meal. The Long Retention of the Barium in the Diverticula Is Obvious. Such Residues Within Diverticula Have Been Observed As Late As the Sixteenth Day After a Barium Meal. (Courtesy of Dr. Jas. T. Case.)

abdomen in a constipated, obese person over thirty-five years of age, accompanied by a spasm of the lower left rectus, and tenderness on pressure in the region of the sigmoid, fever, and a polymorphonuclear leukocytosis, makes the diagnosis of diverticulitis exceedingly probable. If there be chills and if a tumor be palpable, abscess formation is probable, especially if the leukocyte count be high.

In the chronic cases, with infiltration of the wall of the sigmoid (peridiverticulitis) causing slight chronic intestinal obstruction, and imitating carcinoma, a röntgenological study clearly reveals the true nature of the case. The diverticula retain the contrast-substance after it has disappeared from the lúmen of the bowel. Nothing could be more striking than the positive x-ray findings in diverticula of the colon.

Differential Diagnosis.—Diverticulitis must be differentiated (1) from *left-sided appendicitis* (rectal examination, x-rays, Head's zone); (2) from *tuberculous sigmoiditis* (examination of the feces for pus, blood and tubercle bacilli; tuberculin tests; sigmoidoscopy; x-rays); (3) from *dysentery* (search for *Entameba histolytica* or *Bacillus dysenteriae;* x-rays); (4) from *sigmoidal lues* (Wassermann reaction, sigmoidoscopy, x-rays); (5) from *actinomycotic sigmoiditis* (actinomyces fungus in the feces or in the fistulous discharge, x-rays); (6) from *simple catarrhal sigmoiditis* (absence of diverticula on x-ray examination); (7) from *pelvic inflammatory disease* (vaginal examination, contrast-enema).

In *peridiverticulitis,* the condition must be distinguished from other causes of chronic intestinal obstruction, especially (8) from *carcinoma* of the sigmoid (*q. v.*).

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(*d*) *Abdominal Hernias*

Definition.—A hernia is a projection of the viscera from cavities in which they are contained, the lining membrane of the cavity being shoved before them.

Varieties.—When the projection is outward, beneath the skin, or toward it, it is an *external* hernia (subcutaneous, intermuscular, or properitoneal); if it is within the body, in one of the larger body cavities, it is an *internal hernia.*

The **external hernias** include (1) inguinal hernia (*H. inguinalis*), direct or indirect; (2) crural, or femoral, hernia (*H. cruralis*), below Poupart's ligament; (3) umbilical hernia (*H. umbilicalis*); (4) abdominal hernia (*H. abdominalis*), especially in the linea alba (*H. lineae albae*).

The **internal hernias** include (1) diaphragmatic hernia (*H. diaphragmatica*), recognizable in röntgenograms; (2) retroperitoneal hernias, (a) in Treitz's fossa (*H. duodenojejunalis*); (b) in the recessus intersig-

moideus (*H. sigmoidea*); and (c) hernia in the foramen epiploicum of Winslow.

When a hernia cannot be returned, but is fixed say by adhesions or otherwise, it is said to be *irreducible*. The most important complication is *incarceration* (not synonymous with irreducibility), which may lead to *ileus* and to *strangulation*.

Diagnosis.—This belongs to surgery, rather than to inner medicine, and will not be discussed fully here. The practitioner in investigating a case will do well to make a systematic examination, as recommended by de Quervain, as follows: 1. Does a hernia actually exist? 2. Is the hernia incarcerated? 3. What does the hernial sac contain? 4. What is the exact site of the incarceration? 5. In what stage is the incarceration?

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(e) *Enteroptosis*

(*Glénard's Disease*)

Occurrence.—The intestines descend with the other viscera (gastroptosis, nephroptosis, etc.). It is usually a part of Stiller's *asthenia generalis*.

Symptoms.—The methods of studying the position of the intestines have already been described. Though it is true that enteroptosis, and

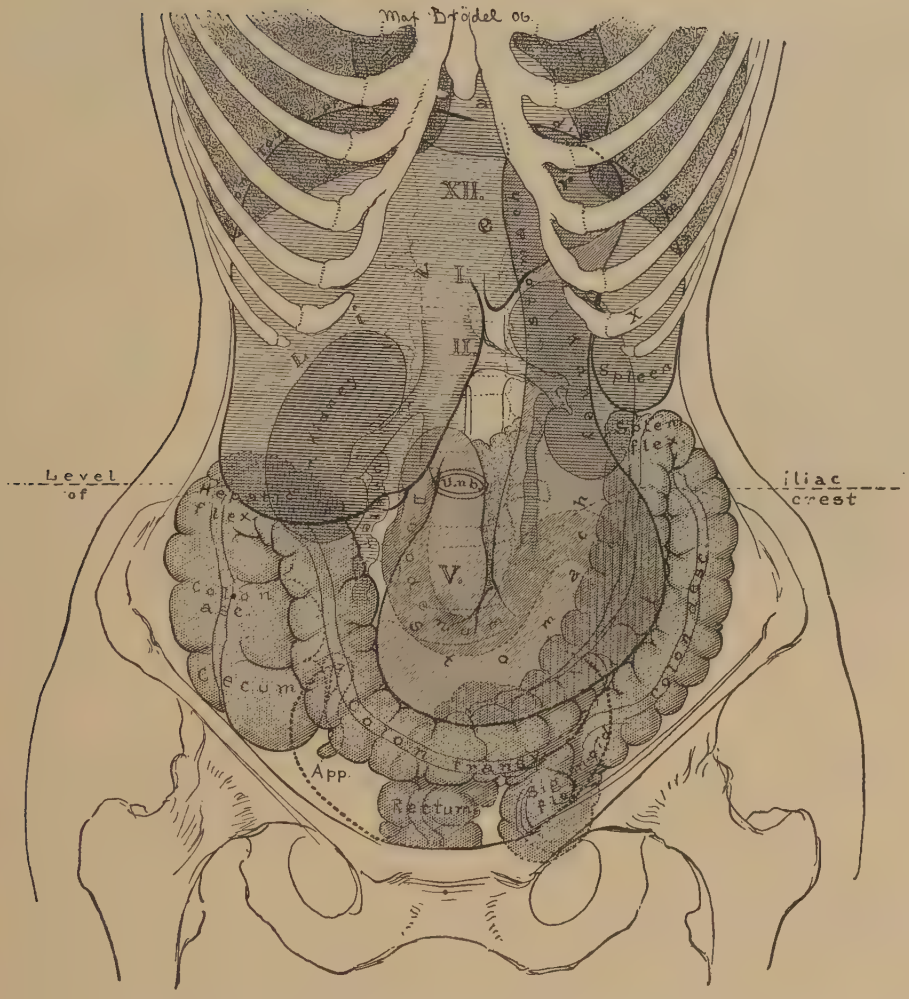

Fig. 412.—Composite Picture from Over 100 Röntgenograms in Possession of Dr. H. K. Pancoast, Showing Displacement Downward of All the Abdominal Organs As the Result of Construction of the Lower Thorax. The Liver Shows Riedel's Lobe; the Stomach Has Descended Into the Pelvis, Carrying the Transverse Colon with It. Note the Hour-glass Contraction of the Fundus of the Stomach. The Right Kidney Has Descended Moderately. (After H. A. Kelly.)

visceroptosis or splanchnoptosis generally, is often associated with neurasthenic symptoms, and with catarrhal conditions of the intestine, it seems likely that far too much weight has been laid upon the importance of gastroptosis and enteroptosis in the recent past. Certainly there has been much overzealous surgery done. The majority of the patients do not require surgical treatment.

Fig. 413.—Marked Redundancy of a Ptotic Transverse Colon. (By courtesy of Dr. Baetjer and Dr. Waters, X-ray Dept., J. H. H.)

Diagnosis.—The exact position of the stomach and intestines in all their parts can now be determined by means of x-ray examinations after a contrast meal and a contrast enema. We now know that a very large proportion of all people examined show more or less enteroptosis, though V-shaped and W-shaped loops of the colon transversum (so-called transversoptosis) can exist without general enteroptosis. It is true that, in certain cases, kinking of the large intestine, due to coloptosis, favors chronic constipation and the development of catarrhal colitis. The condition is best overcome by fattening the patient and, in the meantime, by keeping him at rest or by giving him an abdominal support.

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[Note.—See also References on Gastroptosis.].

4. The Parasitic Enteropathies

The protozoan parasites of the intestine are described under examination of the feces. Here we shall discuss the clinical features of *intestinal helminthiasis and myiasis.*

The principal *worms* that invade the intestine have been described under Examination of the Feces; there, the diagnosis, also, of the worms and their eggs is discussed.

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[Note.—See also References on Parasites in Feces.].

(*a*) *Teniasis*

Symptoms.—Many patients carry tapeworm and are entirely unaware of it. Sometimes, however, severe symptoms occur that disappear after the tapeworm is expelled.

A tapeworm may do injury by directly irritating the mucous membrane, by causing intestinal obstruction, by using up the food supply of the host, and by giving rise to toxins, either those produced by the living worm, or, and more especially, those set free on disintegration of segments within the intestine.

Among the symptoms most frequently complained of, anorexia, capricious appetite, bulimia, salivation, gaseous eructations, nausea, vomiting, abdominal pains, borborygmi, feelings of movement within the abdomen, digestive disturbances, and irregularity of the bowels may be mentioned. In dibothriocephalus invasions, a severe form of anemia of the Addisonian type is not infrequent. A similar anemia is sometimes met with after invasion with Taenia saginata, but it does not occur with Taenia solium.

Nervous disturbances of various sorts are not uncommon. They include visual disturbances (contraction of the visual fields, amaurosis, an-

isocoria), tinnitus aurium, headache, insomnia, fugitive pains, pruritus nasi and pruritus ani. Vertigo is not uncommon, and, occasionally, epileptiform seizures have been reported. In long standing cases, the patient emaciates and abdominal distention develops.

The symptoms of somatic teniasis and of echinococcus disease are described elsewhere.

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(*b*) *Uncinariasis and Anchylostomiasis*

Symptoms.—The symptoms of hookworm invasion vary according to the intensity of the infection and the general hygienic conditions under which the patients live. American observers speak of light, medium and severe infections.

In the *light* infections, the patients may exhibit no noticeable symptoms, though eggs can be found in the feces; such patients are important as **carriers**, as they may keep a region infected and be the source of severe infections of other persons.

In the *medium* infections, a noticeable anemia is present.

In the *severe* infections, the most outspoken phenomena (anemia, mental debility, pot-belly, dirt-eating, etc.) are present.

Sometimes, a fourth class of *very severe* cases, including the patients "in whom death may occur at any moment," is added.

In the *period of invasion,* a cutaneous manifestation, a form of dermatitis, the so-called **ground-itch,** occurring between the toes and on the surface of the feet, sometimes involving the buttocks and other parts of the body, is met with. It is due to the penetration of the skin by the larval worms. Ground-itch is known under different names, such as, *toe-itch, foot-itch, wet-weather-itch,* and *dew-itch;* in Porto Rico, the natives speak of it as *mazamorro,* while among the Cornish miners it is known as *New Sump bunches.* Sometimes ulcers develop on the skin and are slow to heal.

As *the worms develop in the intestine,* symptoms of **indigestion** are common. These include disturbances of appetite (anorexia, bulimia and perverted appetite). The dirt-eaters of hookworm districts illustrate the perversion of appetite. The patients may eat the most peculiar foods (chalk, mortar, mud, clay, rotten wood, resin, paper, etc.). Stiles reports an instance in which a boy ate three coats, thread by thread, within one year. Among the disturbances in the digestive system reported may be

mentioned, salivation, heartburn, nausea, vomiting, abdominal pain and tenderness, flatulence, and irregularity of the bowels. Manifest intestinal hemorrhage is rare, though occult blood can usually be found in the stools.

Perhaps the *most important symptom* in calling attention to hookworm invasion is the pronounced **anemia** that develops. This is of the chlorotic type. The red count falls on the average to two and a half millions, and may fall to below one million. The hemoglobin averages below 50 per cent, the color-index being always low. Regeneration signs, especially polychromatophilia, are usually demonstrable in stained smears. The leukocyte count is usually at the upper limit of normal; sometimes there is a slight leukocytosis; in chronic cases, there may be a leukopenia. The eosinophils are relatively increased, averaging from 10 to 15 per cent of the total white count. In chronic cases with poor resisting power, there may be little or no eosinophilia.

Fig. 414.—Severe Hookworm Case; the Subject is 14 Years Old, But Appears to Be About 7. (After C. W. Stiles, in G. Dock and C. C. Bass' "Hookworm Disease," published by C. V. Mosby Co., St. Louis.)

Symptoms due to the anemia are common. These include, the waxy-white, or dirty yellow, tint to the skin, the edema of the ankles, face and body, the chalky whiteness of the conjunctivae, the dilated pupils, the pulsation in the veins of the neck, the *bruit de diable,* the tachycardia, the dilatation of the heart with hemic murmurs, the dyspnea, the headache, the lassitude, the dizziness, the weakness and "laziness," the polyuria, and the amenorrhea of the victims of hookworm invasion.

When the disease occurs before puberty, the *endocrine functions* may be involved. Signs of hypogenitalism (delayed menstruation; absence of hirci, crines and barbae) are common.

The **mental state** is often deplorable. Many of the backward children in the schools of the South are hookworm cases. Much of the alleged "laziness" in infected districts is due to uncinariasis.

Stiles has emphasized the *economic importance* of the disease, and asserts that uncinariasis is "one of the most important factors in the inferior mental, physical and financial condition of the poorer classes of the white population of the rural

Fig. 415.—Photomicrograph of Necator americanus Sucking the Mucosa. (After W. M. Gray, in G. Dock and C. C. Bass' "Hookworm Disease," published by C. V. Mosby Co., St. Louis.)

sand and piney-wood districts visited." Ashford, King and Gutierrez have laid stress upon the economic importance of hookworm disease in Porto Rico. Incalculable benefits have followed the hygienic propaganda of the Rockefeller Sanitary Commission in infected regions of the United States, and those of the Porto Rican Commission in the Island of Porto Rico.

The *diagnosis* of uncinariasis has been described in connection with the description of the worms (see Examination of the Feces).

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[Note.—See also References under Intestinal Worms.].

(*c*) *Strongyloidosis*

Invasion with *Strongyloides stercoralis* or the *Cochin China Worm* is more common in the United States (Thayer, Strong) than is generally supposed, but it is very much more widespread in India, where it is a common cause of anemia.

Invaded patients may show in some instances almost no symptoms; in others, severe symptoms develop. When the worms are present in large numbers, there is usually, according to Strong, an intermittent diarrhea with intestinal disturbances, and, pathologically, a catarrh of the small intestine.

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(*d*) *Ascariasis*

Symptoms.—Many children with round worms present no noticeable symptoms. Even when symptoms are present, they are so vague that they may not excite suspicion of their cause. Most of the symptoms depend either upon direct irritation of the intestinal mucous membrane, or upon reflex nervous disturbance.

The symptoms include pruritus nasi, gritting of the teeth, anorexia, hiccough, capricious or perverted appetite, nausea, vomiting, colicky pains in the abdomen, borborygmi, irregularity of the bowels, signs of intestinal obstruction, pruritus ani, pallor, dark rings about the eyes, fretfulness, choreiform movements, convulsive seizures, neurasthenic and psychotic states, progressive emaciation, etc.

Among the most interesting of the conditions due to ascariasis are those dependent upon the habit of *wandering* exhibited by the so-called **erratic eel-worms.** A wandering worm may enter the mouth, the nose, the eustachian tube, the larynx, trachea and bronchi, the bile ducts, the pancreatic duct, or the urinary passages. Sometimes they cause serious symptoms. Thus, they may perforate through an ulcer into the abdominal cavity; on entering the lung, they may be the cause of abscess or gangrene; or, occasionally, they bore through the abdominal wall, appearing most often at the groin (in adults) or at the umbilicus (in children).

[Note.—For references see under Intestinal Worms.]

(*e*) *Oxyuriasis*

Symptoms.—Pinworms are often discovered accidentally, the invaded children not complaining of symptoms. When the worms are numerous, however, there is intense pruritus ani, especially on going to bed at night, when the female worm starts to wander. On *inspection,* there is redness and irritation about the anus. Within the bowel, an intestinal catarrh is set up, causing diarrhea and tenesmus. The little patients become restless and sleepless; headache and vertigo are not uncommon. Choreiform movements and convulsive seizures sometimes occur. Occasionally the worms cross the perineum and enter the vagina where they set up a mild vaginitis, with hyperesthesia and leukorrhea. They have also been known to enter the uterus and even the abdominal cavity.

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(*f*) *Trichocephaliasis*

As a rule invasion with whipworm does not cause symptoms. In severe cases, however, *anemia* of a grave type may develop, associated with *digestive disturbances* and *nervous symptoms.*

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Fig. 416.—Schematic Drawing to Show Method of Invasion of Trichinella spiralis. The Villus on the Left Shows the Cross Section of Two Parasites Piercing the Epithelium Obliquely. The Male Parasite Touching the Three Middle Villi Shows How One Parasite May Pass to Several Villi, How It Never Goes Into the Connective Tissue and How the Peeled Off Epithelium Becomes Necrotic. In the Right Hand Crypt Is an Adult Female Trichinella that Has Penetrated to the Bottom of the Gland and There Started Out Again. The Epithelium Where Peeled Off Is Necrotic. An Embryo Is Shown As Being Born Between the Epithelium and Connective Tissue. Here Again the Adult Parasite Does Not Penetrate the Connective Tissue. (After C. Frothingham, Arch. Int. Med.)

(*g*) *Trichiniasis*

Symptoms.—Rupprecht has divided the course of the disease that follows the eating of pork infected with *Trichinella spiralis* into three periods; these periods correspond to the three stages through which the parasite passes and their respective locations.

In the **period of ingression,** the *adult* parasites are in the intestine, and if any symptoms are present, *gastro-intestinal symptoms* predominate. Within the first day or two after eating the raw or rare pork, a heavy feeling in the stomach, with gaseous eructations, nausea, and, perhaps, vomiting, develops. There is anorexia, with irregularity of the bowels, usually diarrhea. There may also be colicky pains in the abdomen. About the 8th day, there is a temporary *first edema* of the eyelids and face, which lasts from two to five days. Wandering embryos can be found in the serous cavities from the 7th to the 8th day on.

In the **period of digression,** beginning between the 9th and the 14th day (occasionally as late as six weeks after infection), the *embryos* wander to the muscles and attack them, setting up a *myositis,* which characterizes the symptoms of this period. The muscles, especially the M. biceps brachii and the M. gastrocnemius, present an increased consistence, are tender on pressure and on extension of the forearm and leg, so that the patients keep the limbs in a position of semiflexion. Any movement may be painful (chewing, speaking, breathing, and moving the eyes). The aphonia and dyspnea are in some cases extreme.

In the **period of regression,** which corresponds to that of *encystment of the larval parasites,* all the symptoms are at first exaggerated. About the twenty-fourth day a *second edema* develops, which affects the head and is present in nearly all cases, giving the disease one of its colloquial names, "disease of the big head." The patients at this stage often look cachectic and anemic.

There is some *fever;* during the myositis, the fever may be high (104° to 106°), and last for from two to six weeks, being often mistaken for typhoid fever. There is *anorexia,* and, also, *thirst.* In the early stages, there is *oliguria,* during convalescence, *polyuria;* as a rule, there is no albuminuria. *Mental symptoms* may be marked (insomnia, delirium, occasionally somnolence or coma).

The *death rate* varies exceedingly, averaging between 5 per cent and 10 per cent; in some epidemics it is very high, nearly all of those affected dying. Death usually occurs from the fourth to the sixth week (during the period of myositis).

Diagnosis.—Trichiniasis, it should be remembered, occurs, as a rule, in *groups of cases,* so that small epidemics resembling typhoid fever, and occurring in a single family or neighborhood, and, especially, after picnics or celebrations at which pork has been eaten, should make one think

of the possibility of trichiniasis. *Isolated cases* are often mistaken for muscular rheumatism or for typhoid fever. The disease may occur in any class in the community.

If trichiniasis be suspected, the routine investigation recommended by Stiles should be followed:

1. Examine any of the *pork* left for encysted larvae by mincing it finely, washing it in water to remove the salt, and feeding it at once to two or three small animals (rabbits, guinea-pigs, or white rats), never to wild mice or rats. One of the animals should be killed at the end of two or three days, and the contents of the upper part of the small intestine examined for adult worms. A second

CHART I.

Fig. 417.—Chart Showing Changes in the Number of Eosinophile Leukocytes Caused by Infection with 3,000 Trichinae. The Percentage of Eosinophile Leukocytes in the Blood Is Indicated by a Dotted Line; Their Number in 1 c.mm. by a Broken Line; the Weight of the Animal by a Continuous Black Line. (After E. L. Opie, "Studies from the Rockefeller Inst. for Med. Res.," Extracted from the Am. J. M. Sc.)

animal should be killed at the end of two weeks, and a third at the end of three weeks, and the muscle of the diaphragm of these animals examined for larvae.

2. As soon as trichiniasis is suspected, examine the *stools* of the patient for discharged adult worms, by diluting the feces with warm water in a tall graduate, shaking well, and then allowing the worms to settle to the bottom. The supernatant fluid is poured off and the sediment placed in a shallow glass dish, in a layer less than one-twelfth of an inch thick; this is moved gently over a dark background, the dish being tipped first to one side and then to the other; if small, hairlike objects tending to cling to the glass are observed, they can be placed in a drop of water on a glass slide, a cover-slip applied, and an examination made under a low-power lens.

3. Make a total *count of the white blood corpuscles* and make smears and stain for a *differential count* in order to discover an *eosinophilia* if present. Dr. T. R. Brown's observation of outspoken eosinophilia in trichiniasis has greatly facilitated the recognition of the disease.

4. If by the third week or later the diagnosis be still uncertain, and if trichiniasis be still suspected, a *small piece of muscle should be excised*, preferably from the M. deltoideus, teased on a glass slide, a drop of water and glycerin added, a cover-glass applied with gentle pressure, and an examination made under a low power of the microscope for larvae.

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(*h*) *Myiasis*

From early times on, medical men have reported invasions of human beings with the larvae of insects, most often by fly-larvae (*myiasis*).

Wounds of the skin are sometimes invaded (*myiasis externa*), but the larvae are met with more often in the nose, the stomach, and the intestines (*myiasis interna*). The diagnosis is made by finding the larvae in the vomitus or in the feces.

One of the most dangerous forms of external myiasis is that due to the larva of *Compsomyia macellaria,* known as the "Texas screw-worm." For a full list of larvae parasitic for man, see Gilbert's article.

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5. The Neoplastic Enteropathies

Tumors or neoplasm of the intestine may be malignant or benign. Of the malignant tumors the more important are carcinoma, sarcoma, and lymphosarcoma; of the benign tumors met with here, adenoma (polyp) and lipoma are the commoner, fibroma, myoma, angioma, and gaseous cystic tumors being only rarely met with.

(*a*) *Carcinoma of the Intestines*

Etiology.—The cause is entirely unknown. Men are somewhat more often affected than women. It is a disease of older people (40 to 60), though one-sixth of all cases of cancer of the intestine occur between the 30th and the 40th year, and one-seventh before the 30th year. This relatively early occurrence of cancer of the bowel is an important fact to bear in mind; it may occur even in infancy.

Site.—Cancer of the intestine most often occurs in the rectum, less often in the colon sigmoideum, at the colonic flexures and in the cecum; occasionally, in the vermiform process, in the duodenum, and in the jejunum.

Pathology.—Cancer of the intestine is almost always primary. As to type, adenocarcinoma beginning in the columnar epithelium of the glandulae intestinales (Lieberkuehni) is the most common, though medullary, colloid, and scirrhous carcinomata also occur. Epithelioma may develop in the pars analis recti.

In *form* the growth may be nodular, annular, or an ulcerative cauliflower growth. Intestinal obstruction is often caused by cancer.

Cancerous growths often *extend* through the wall of the gut to the peritoneum

and may be the cause of peritoneal adhesions, of perforation with abscess-formation, or of a carcinosis peritonei with hemorrhagic exudate ("bloody ascites"). In advanced cases, there is often *fistula-formation* (rectovesical, rectovaginal, entero-abdominal).

Metastases in other organs occur sooner or later, though fortunately it is sometimes possible to recognize cancer and remove it before metastasis takes place.

Fig. 418.—Great Dilatation of the Small Intestine Due to Carcinoma at Ileocecal Junction. The Röntgenogram Was Made 24 Hours After the Bismuth Meal Was Ingested. (By courtesy of Dr. Baetjer and Dr. Waters, X-ray Dept., J. H. H.)

The metastases involve the regional lymph glands and the liver most often, the omentum, mesentery, lungs, or kidneys less frequently.

Symptoms.—The two principal general symptoms are *anemia* and *cachexia*. *Fever* is present after ulceration begins. There may be either diarrhea or constipation. A careful examination of the *feces* may reveal

blood or pus or both, and, rarely, tumor particles. Symptoms of intestinal *obstruction* with colicky pains, usually chronic, occasionally acute, sooner or later appear.

On physical examination, a *tumor* may be palpable either in the abdomen, or in the rectum. Abdominal tumors of cancerous nature are very *mobile* on palpation; they are most often found in the left iliac fossa (sigmoid cancer) or in the right iliac fossa (cecal cancer); feces often accumulate proximal to the cancerous growth. Digital examination of the rectum and vagina, and rectoromanoscopy suffice for diagnosis of cancer of the rectum and lower sigmoid.

Röntgenological examination after a contrast enema or a contrast meal (*q. v.*) is exceedingly valuable in the diagnosis of cancer. In the accompanying figure is shown a röntgenogram illustrating dilatation of the small intestine due to cancer at the ileocecal junction.

i. Carcinoma of the Rectum

This is the commonest cancer of the intestine. There is *pain,* worse on defecation; it is felt in the rectum, and extends to the sacrum behind, the bladder and genitals in front, or it may appear as a sciatica. *Tenesmus* develops; on ulceration, the *feces* contain blood, pus, and mucus. There is usually constipation, sometimes diarrhea. The sudden development of *hemorrhoids,* at middle life or later, in a person previously free from them should make one suspect beginning carcinoma. The growth can usually be felt on *digital examination.* If there be doubt as to its nature, a small piece may be excised for histological examination before radical operation is undertaken.

Carcinoma recti should be differentiated (1) from *polyposis recti* (childhood, soft, movable, pedunculated; histology); (2) from *tuberculosis recti* (flat, painful ulcer of pars analis recti; histology; tuberculosis elsewhere, often fistula in ano); (3) from *stricture due to gonorrheal or luetic proctitis* (smooth-walled, rigid, cylindrical tube, admitting the finger, the tissue unyielding; complement-fixation tests; anamnesis); (4) from *inflamed hemorrhoids* (subjective symptoms, periodic hemorrhages, inspection and palpation).

ii. Carcinoma of the Colon sigmoideum

Rare before the 50th year. Mobile mass in left iliac fossa. Sigmoidoscopy, rectal injection, and, above all, röntgenography are diagnostic. The condition must be differentiated especially from benign *peridiverticulitis* (x-rays).

iii. Carcinoma of the Intestinum cecum

The *general symptoms* of cancer along with the existence of a *mobile tumor* in the right iliac fossa are highly suggestive. Cancer here must be differentiated (1) from *peri-appendiceal abscess;* (2) from *cecal tuberculosis,* and (3) from *fecal accumulation.*

iv. Carcinoma of the Duodenum

This is rarely seen. Males, past middle life, are most often affected. The pars descendens duodeni is most often involved. Boas' classification of cancers here is helpful; he distinguishes (1) suprapapillary, (2) circumpapillary, and (3) infrapapillary cancers, according to their relation to the papilla duodeni (Santorini). In the *suprapapillary* form, the symptoms closely resemble those of pyloric stenosis; in the *circumpapillary* form, there is jaundice, often without pain or gastro-intestinal symptoms; and in the *infrapapillary* form, gastric symptoms predominate, and the vomitus contains bile and pancreatic juice.

In duodenal cancer, the pain is in the right hypochondriac region, and, sometimes, a tumor is palpable there.

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(*b*) *Sarcoma and Lymphosarcoma of the Intestine*

Tumors of this type occur here less often than carcinoma; they are met with as a rule before the age of 40. Lymphosarcoma, originating in the lymphatic nodules, is most often found in the small intestine; ordinary sarcoma, originating in the submucosa, equally often in the large, and the small, bowel.

Sarcoma, except in the rectum, does not cause obstruction but rather dilatation of the lumen of the intestine.

Symptoms.—There is a very rapid deterioration of the general health, without local symptoms, except a palpable tumor. Death occurs, as a

rule, within a year from onset. Metastasis occurs so early that operation is rarely of any service.

The condition should not be confused with Hodgkin's disease (an inflammation, not a neoplasm), which sometimes involves the intestine.

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(c) *Polyposis intestinalis*

(Polyps of the Intestine, Polyadenomatosis intestinalis)

Mucous polyps of the rectum in children, and villous polyps in adults have long been known clinically. Recently, a polyposis intestinalis adenomatosa diffusa has been described by Scagliosi. For the diagnosis of rectal polypi, see above under Carcinoma recti.

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6. The Congenital Enteropathies

Under this heading we may mention (1) Congenital malpositions; (2) Megacolon congenitum (Hirschsprung's disease), and (3) Meckel's diverticulum.

(a) *Congenital Malpositions of the Intestines*

In *situs inversus totalis*, the stomach and intestines occupy a position corresponding to a mirror-picture of the normal; the spleen is in the right, and the liver in the left, hypochondrium; and the thoracic organs are similarly transposed.

In *situs inversus partialis*, the abdominal viscera are transposed, though the thoracic organs are in their normal positions.

Congenital malpositions of the intestine alone occur and may be very important in abdominal diagnosis. The four main forms are: (1) the large intestine lies wholly behind the small intestine, owing to failure of the umbilical loop to rotate—*retroposition;* (2) the large intestine lies in the left side of the abdominal cavity, owing to incomplete rotation of the umbilical loop—*sinistroposition;* (3) the large intestine lies in the right half of the abdomen, owing to partial rotation of the umbilical loop in the wrong direction—*dextroposition;* and (4) there is complete crossing of the small and large intestine, but the position is abnormal, owing to complete rotation of the umbilical loop but in the wrong direction (*situs inversus abdominalis partialis inferior*).

As de Quervain emphasizes, the practically important features are (1) the position of the vermiform process, and (2) the crossing of the small and large intestines. Taking the several malpositions together, the *appendix may come to lie in any part of the abdomen!*

The matter of the crossing of the small and the large intestine may be important in performing gastro-enterostomy. Ordinarily, the surgeon seeks the uppermost loop of the small bowel where it passes beneath the transverse colon; if the normal crossing have not occurred, it will be necessary to follow the duodenum in order to find the beginning of the jejunum. In sinistroposition of the large intestine, the duodenum passes toward the right kidney, and goes over into the jejunum in the right iliac fossa (de Quervain).

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(*b*) *Hirschsprung's Disease*

(*Megacolon congenitum, Idiopathic Dilatation of the Colon*)

Definition.—A persistent, high-grade dilatation of the colon, with thickening of all the tunics of the wall, especially of the tunica muscularis, with retention of large quantities of fecal matter.

Etiology.—The congenital condition is met with chiefly in young boys. Its nature is not wholly clear, though a congenital abnormality of the colon is usually held to be responsible. Some assert that an acquired form also occurs, due most often to kinking as a result of the sinking of a long sigmoid loop, filled with feces, into the pelvis; patients with megasigmoid are always in danger of ileus (Frank).

Fig. 419.—Giant Colon in a Twelve-year-old Boy. (Med. Service, J. H. H.)

diarrhea or by artificial emptying of the colon. a contrast enema is helpful in diagnosis.

Symptoms.—The abdominal enlargement may be extreme. A patient described by Formad had a colon, the contents of which weighed 47 pounds; the man was exhibited as a monstrosity, and was known as the "balloon man." The enlargement affects specially the upper half of the abdomen so that the lower aperture of the thorax is widened and the umbilico-xiphoid measurement increased. As the patient emaciates, the outline of the colon is visible as a pattern through the abdominal wall; often the outlines of the teniae coli and of the haustra coli can be distinguished. The patients are constipated. As the distention from feces grows greater, attacks of pain occur, relieved by X-ray examination after

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(c) *Persistent Meckel's Diverticulum*

The omphalomesenteric duct sometimes persists and is known as Meckel's diverticulum. It is situated on the convex side of the small intestine about 1 meter above the valvula coli. It is usually 3 to 10 cm. long, but may be 25 cm. long. Rolleston found it in 10 out of 337 cases examined, and 9 of these were males. The end usually lies free in the abdominal cavity, but sometimes it remains attached at the umbilicus; or it may become adherent to various structures, most often the mesentery. Loops of bowel may be caught beneath such an adherent diverticulum and acute or chronic intestinal obstruction result. A diverticulum with free tip may be the starting point of an intussusception, or the site of a volvulus. The diverticulum may perforate and cause an abscess in the median line, or to the right of it below the navel.

7. The Nervous Enteropathies

(*The Intestinal Neuroses*)

Under this heading are included certain disturbances that depend predominantly upon abnormal innervations of the intestines. These abnormal innervations may in turn be of reflex origin, or they may be secondary to pathological cerebrospinal states. Many of them appear to depend upon lack of balance in the autonomic innervations, due to the existence of either a sympathicotonic or a vagotonic state.

These perversions of intestinal innervation are divisible into (1) motor, (2) sensory, and (3) secretory intestinal neuroses. Combinations may, of course, occur.

(a) *Disturbances of Motor Innervation of the Intestines*

These include:

1. **Peristaltic unrest,** or **tormina intestinorum,** in which there are excessive peristaltic contractions of the intestines, sometimes with visible and audible movements. The noises produced can often be heard at some distance from the patient, so as to be very embarrassing to him. As a rule, the movements are painless. The condition must not be confused with chronic intestinal obstruction with abnormal peristalsis proximal to it.

2. **Hypermotility of the intestine.**—This may cause a nervous diarrhea, on the one hand, or a spastic constipation, on the other.

3. **Paralysis of the intestine.**—This may be secondary to a mechanical ileus, or may be primary, as in the dynamic ileus already described.

4. **Paralysis of the M. sphincter ani.**—This is usually a sign of organic disease (see Nervous System), but, in rare instances, it is met with as a functional neurosis that is curable.

(*b*) *Disturbances of Sensibility of the Intestine*

Under this heading are included:

1. **Hyperesthesia of the intestine,** in which the intestinal processes normally unfelt become appreciated by the patient as sensations of fullness, stabbing, burning, or tearing; sometimes these feelings are associated with interpretative delusions as to their cause. The psycho-analysts make much of abnormal sensations and emotions in anal and rectal domains.

2. **Neuralgias of the intestine.**—These have been described under various names (*nervous enteralgia, neuralgia mesenterica, hypogastric neuralgia*). By neuralgia, is not meant a colic due to spasm of the wall, but a true primary painful affection, characterized by violent attacks of pain in the abdomen. Head's zones may be demonstrable on the skin and be helpful in localization of the loops involved. The exact nature of these neuralgias remains to be worked out, and especially their relations to lead-colic and the tabetic crises of the intestine and rectum.

(*c*) *Disturbances of Secretory Innervation of the Intestines*

These include the *increased* secretion that occurs in nervous diarrhea, the *decreased* secretion that accompanies some forms of constipation, and especially the *perverted* secretion known as mucous colic.

i. Mucous Colic

(*Enteritis membranacea, Tubular Diarrhea, Membranous Colitis*)

Definition.—By mucous colic is meant a condition in which an excess of mucus is produced in the colon, usually periodically; it is associated with painful spasms that are accompanied, or followed, by the expulsion of mucus in the feces, either in masses, strings, or as tubular casts of the intestine; the gastro-intestinal functions are disturbed, and there is usually marked nervous depression accompanying the attacks.

Etiology.—The disease is commonest in nervous women around middle life. Its cause has been much disputed. Many hold it to be a pure neurosis, occurring in neurasthenic, hysterical, and hypochondriacal patients. Others regard it as symptomatic of visceroptosis. Still others look upon it as a metabolic disturbance associated with gout or the arthritic diathesis.

It seems probable that, in the majority of instances, a neuropathic tendency is a prerequisite to the disturbance, but the actual attacks often depend either upon fecal accumulation in a ptotic intestine, or upon reflex irritation from a chronic appendicitis, a cholecystitis, or a duodenal or gastric ulcer. Gouty persons seem to be especially predisposed. Other reflex causes include prostatic irritation, rectal irritation, and, in the female, pelvic inflammations of various sorts.

Symptoms.—In a typical attack, the patient becomes gloomy and depressed, is constipated, and begins to pass ribbonlike stools; the colon often becomes distended, there is increasing uneasiness in the abdomen, and, after a day or two, an attack of abdominal pain of considerable violence occurs, followed by the passage of masses of mucus, or of a mucous cast. The symptoms may then be relieved, though, in some cases, the depression continues for a day or two, and a feeling of rawness or soreness in the abdomen persists. After an attack is over, the patients sometimes feel better than they have felt for some time earlier.

In addition to the symptoms that accompany the attack, these patients present other gastro-intestinal, nervous, and nutritional disturbances.

Of the *gastro-intestinal* symptoms, anorexia or capricious appetite is common. The patients restrict their diet in the hope of relieving their symptoms. They often suffer from the group of symptoms ordinarily designated as nervous dyspepsia. Constipation, usually of the spastic type, is nearly always present in these patients.

The *nervous symptoms* are usually marked. The patients are neurasthenic, hypochondriacal, or hypomelancholic; they are depressed, gloomy, and irritable. Headache, especially migraine, neuralgias, and tachycardia are common.

The *state of nutrition* is usually below par. As a rule, the patients are thin, often 25 to 50 pounds below their calculated ideal weight. Though they look pale, the hemoglobin-content may be normal.

The *passage of intestinal sand* in patients who suffer from mucous colic is not uncommon. Chemically, the sand consists of phosphates, oxalates and carbonates of lime, magnesium and iron. It is interesting that, in some women, membranous mucous colic is associated with membranous dysmenorrhea and membranous cystitis.

Diagnosis.—The history of the attacks and the finding of the characteristic mucus in the stools is diagnostic. An x-ray examination will often reveal precisely the portion of the bowel affected.

It is exceedingly important in symptomatic mucous colic to look for a primary cause (chronic appendicitis; cholecystitis; various causes of chronic intestinal obstruction). But many of the cases must be regarded as primary; in them, especially, atropin seems to be helpful, and it is

surprising how many of these patients regain tolerable health if general upbuilding measures be employed, and the patients be systematically fattened, and psychotherapeutically reëducated.

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F. Special Diagnosis of Diseases of the Pancreas

Among the principal diseases of the pancreas are:

I. The *inflammatory pancreatopathies* (acute hemorrhagic necrosis; acute hemorrhagic pancreatitis; gangrene of the pancreas; suppurative pancreatitis and peripancreatitis; and chronic indurative pancreatitis).

II. The *pancreatopathies of circulatory origin* (pancreatic apoplexy; atherosclerosis of the pancreas; granular atrophy of the pancreas due to arteriolar sclerosis).

III. The *neoplastic pancreatopathies* (carcinoma pancreatis; cystic tumor of the pancreas).

IV. *Diseases of the pancreatic ducts* (pancreatic calculi; ascending sialoangitis; ranula pancreatis).

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1. The Inflammatory Pancreatopathies

Under this heading will be described both the acute and the chronic inflammations of the pancreas.

(*a*) *Acute Hemorrhagic Necrosis; Acute Hemorrhagic Pancreatitis; Gangrene of the Pancreas*

Definition.—A primary necrosis of the pancreas, followed by hemorrhage into the pancreas and peripancreatic tissue, the development of an acute inflammation of these tissues, and sometimes of gangrene; more rarely there is abscess formation.

Etiology.—The condition depends upon the activation of the ferments of the pancreatic secretion within its own ducts, being most often due to the entrance of bile or of duodenal contents into the ducts.

The condition is more common, and more rapidly fatal, in men than in women (about 2:1). It occurs most often in middle life (30th to 50th year). The conditions that favor the entrance of bile into the pancreatic ducts are *cholelithiasis*, especially a calculus lodged near the termination of the ductus choledochus, and other *obstructions at the papilla duodeni* (duodenitis, neoplasm). The condition sometimes follows a direct blow in the epigastric region (traumatic pancreatitis). On account of the frequent association with gall-stones, it is not surprising that the condition is prone to occur in *obese* persons.

Pancreatitis has been produced experimentally by the injection of artificial gastric juice into the pancreatic ducts of dogs (Hlava), and by the introduction of cultures of various bacilli, of diphtheria toxin (Carnot), and of weak solutions of acids and alkalis (Flexner).

The human disease does not appear to be due to bacterial invasion, though, if abscess follow, it depends upon infection of the necrotic tissue with pyogenic bacteria.

Pathology.—The activated pancreatic juice causes an initial necrosis. This is followed by hemorrhage and the development of violent inflammation. Should the patient survive long enough, the pancreas becomes transformed into a soft, black, friable mass (gangrene), and may undergo complete sequestration. The fat in and about the pancreas, and in the wall of the bursa omentalis, shows confluent and isolated areas of **fat-necrosis** in the form of characteristic opaque white foci, which are in marked contrast with the normal translucent abdominal fat. The fat-necrosis is due to the action of free lipase derived from the activated pancreatic secretion. Lipase has been demonstrated in the necrotic foci by S. Flexner, and fat-necrosis has been produced experimentally in cats and dogs by watery extracts of the pancreas (H. G. Wells). A knowledge of the appearance of fat-necrosis in the abdomen is essential to the surgeon, for if it be found on opening the abdomen it is nearly always due to an acute hemorrhagic, or a gangrenous, pancreatitis.

If pyogenic infection complicate a hemorrhagic pancreatitis, an abscess will form, confined as a rule within the walls of the bursa omentalis. Occasionally, an abscess cavity extends so as to form a pocket behind the peritoneum in front of the left kidney. An abscess may perforate into the stomach, duodenum or jejunum.

Symptoms.—The onset of **hemorrhagic necrosis with acute pancreatitis** is, as a rule, sudden, with *severe pain* in the epigastrium and marked shock. In the fulminating cases, death may occur within a few days. In

about half the cases, death occurs within the first five days; in the other half, the process is subacute and death may not occur until after weeks or months have elapsed; some patients recover.

In the anamnesis, about half the patients give a history of *preceding attacks of indigestion* (abdominal pain, nausea, vomiting); about one-fifth of the cases have earlier suffered from typical *attacks of biliary colic.* Sometimes, however, robust, obese persons, previously entirely healthy, are affected.

The *pain at onset* is usually in the middle line just above the umbilicus, but it may be situated further to the left, and, in some cases, is most marked in one or other hypochondriac region, or even in the lower abdomen. There is marked *tenderness* on pressure, and *rigidity* of the upper recti. *Vomiting* sets in and recurs at brief intervals; the vomitus usually contains bile, and, sometimes, blood. The *shock* to the nervous system is obvious (tachycardia, cyanosis, weakness). No tumor mass is palpable. There may be either constipation or diarrhea. In the constipated cases the condition may be hard to differentiate from acute intestinal obstruction. The *feces* are often clay-colored; they do not, as a rule, contain blood or an excess of fat. The diastase of the feces may be greatly diminished, while that of the urine is increased. In about one-tenth of the patients, *jaundice* is present. There is, as a rule, no fever at first. There is, however, an outspoken *leukocytosis.* Glycosuria rarely occurs.

Patients that survive the early period just described become examples of **gangrenous pancreatitis.** About the 4th day, the early symptoms diminish in violence, the constipation lets up, and the symptoms characteristic of gangrene of the pancreas appear, namely, fever (100°–104° F.), and a palpable *epigastric tumor.*

The leukocytosis persists in gangrene, even should the temperature stay normal. The tumor mass, palpable in the epigastrium, is due to presence of exudate within the bursa omentalis. As a rule, it is first demonstrable on the left side (left hypochondrium and flank); later, it becomes palpable between the stomach and the colon (in the epigastrium). The mass becomes more distinct as the patient emaciates and as the muscle spasm of the early stage lets up. Inflation of the stomach and of the colon may help to localize the mass.

In the gangrenous stage, the proportion

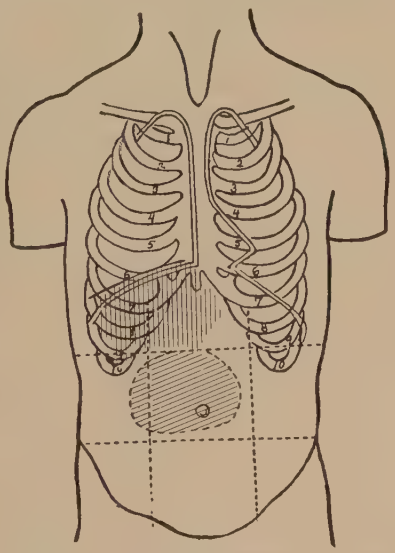

Fig. 420.—Position of Tumor in a Case of Acute Pancreatitis. (After W. S. Thayer, J. H. H. Bull.)

of split fat in the feces may be markedly diminished (von Noorden). In rare cases, necrotic pancreatic tissue may be passed in the feces (Chiari). Jaundice is present in one-fifth of the cases (Fitz).

Among the serious **complications** that may *develop,* the three most important are (1) *abscess* in the bursa omentalis; (2) *thrombosis* extending to the splenic and portal veins, and (3) *perforation* of the stomach, duodenum, jejunum, or transverse colon (Thayer). Among the **sequelae,** *pseudocyst formation* appears to be the most common. Glycosuria is rarely observed, even in the patients that recover.

Diagnosis.—The mode of onset (sudden, violent epigastric pain, vomiting, shock), especially in a fat man who has had a history of gall-stone attacks, is very suggestive. Examination of the feces is rarely of much help in the diagnosis, though a diminished diastase-content or an increase of the split fat may be suggestive. The presence of lipase in the urine, or an increased diastase-content in the urine, may be corroborative points.

In the *differential diagnosis,* we must rule out (1) *acute intestinal obstruction,* (2) *simple biliary colic,* (3) *acute peritonitis due to perforation of the stomach, duodenum* or *gall-bladder,* and (4) *rupture of abdominal aneurism.*

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(b) *Purulent Pancreatitis or Peripancreatitis*

(Pancreatic Abscess; Peri-pancreatic Abscess; Abscess of the Lesser Peritoneal Cavity; Abscess in the Bursa omentalis; Suppurative Pancreatitis)

Etiology.—Suppurative pancreatitis may be due (1) to secondary bacterial invasion after hemorrhagic necrosis or gangrene of the pancreas; (2) to extension of an abscess from an adjacent organ; (3) to metastatic infection through the blood vessels; or (4) to ascending pyogenic infection through the pancreatic ducts.

The first and fourth are the commonest types. Ascending infection occurs most often in association with gall-stones, pancreatic calculi, or malignant growths compressing the duct.

Symptoms.—These vary with the cause. In about half the cases, the onset is like that of acute hemorrhagic necrosis and is then most often due to this condition; after the acute symptoms diminish, the symptoms of suppuration (fever, palpable abdominal mass, chills, leukocytosis, progressive weakness, emaciation) develop.

In some cases, there is a gradual onset with moderate abdominal pain and symptoms of gastro-intestinal indigestion. Later, the signs of pyogenic infection become obvious.

Involvement of the bursa omentalis in the suppuration is common. Rupture into the general peritoneal cavity does not often occur. Frequently, adjacent organs become adherent, and sometimes the abscess breaks into hollow viscera, with formation of fistulous communications with the stomach, duodenum or colon. Thrombophlebitis and thrombosis of neighboring veins may occur.

Diagnosis.—It is often impossible to decide whether we are dealing with gangrene of the pancreas following acute hemorrhagic necrosis, or suppurative pancreatitis; but as surgical interference is indicated in both cases, this is not so very important. Confusion with cyst of the pancreas,

or with carcinoma pancreatis, should rarely occur, since, in abscess, the symptoms come on rapidly and are severe.

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(c) Chronic Indurative Pancreatitis

Definition.—By chronic pancreatitis is meant a chronic inflammation of the pancreas leading to more or less destruction of the parenchymatous tissue, with increase of the connective tissue.

Forms.—Two types are distinguished: (1) *chronic interlobular pancreatitis,* a true chronic inflammation, as a rule secondary to obstruction, or to ascending infection of the pancreatic ducts; in this form, the lobules of the gland are but little invaded in the early stage, though in the late stages there may be extensive destruction of the gland substance; the islands of Langerhans suffer but little, at any rate early in the disease; and (2) a *chronic interacinar pancreatitis* (Opie), in which the new connective tissue penetrates between the acini, and the islands of Langerhans are involved, even in the early stages. There seem to be two forms, in turn, of this interacinar type, one, a true chronic inflammation, the other an atrophy dependent upon arteriolar sclerosis; indeed, the condition is not unlike contracted kidney, which may, on the one hand, be a true chronic nephritis, and, on the other, a renal atrophy dependent upon arteriolar sclerosis. In association with hemachromatosis, the chronic pancreatitis that occurs is of the interacinar type, involving the islands of Langerhans; this explains the frequent occurrence of diabetes (*diabète bronzé*) with this condition.

Etiology.—Opie has analyzed the cases in the Johns Hopkins Hospital. Of 30 patients, 17 were males, and 13 females. Death occurred after the fortieth year in five-sixths of the cases. In two-thirds of the cases, the condition appeared during the fifth and sixth decades. Its late appearance is doubtless due to its association with gall-stones, carcinoma, and cirrhosis of the liver, on the one hand, and with atherosclerosis, on the other.

The *chronic interlobular form* is due to partial or complete occlusion of the ductus pancreaticus (from pancreatic calculi, gall-stones, carci-

noma, or other new growth). At operations for gall-stones, induration of the head of the pancreas is not infrequently found, and may be mistaken for carcinoma. In some instances, ascending infection of the pancreatic duct, secondary to infection of the biliary passages, may cause a chronic pancreatitis in the absence of obstruction to the pancreatic duct.

In the *chronic interacinar form,* the most common cause appears to be arteriolar sclerosis leading to atrophy and to increase of the interstitial tissue. In the cases associated with atrophic cirrhosis of the liver, the two conditions may perhaps have the same etiology (alcoholism, chronic infection, etc.).

It seems to me likely that the interacinar type should be removed from the group of inflammatory pancreatopathies and placed among the pancreatopathies of circulatory origin.

Symptoms.—Chronic pancreatitis, of itself, produces no symptoms, except when the induration causes (1) compression of the bile duct where it passes through the head of the pancreas, or (2) destruction of the islands of Langerhans, so that diabetes develops.

The other symptoms that have been observed in pancreatitis (epigastralgia, vomiting, emaciation, fatty stools, etc.) are due less to the chronic pancreatitis itself than to the diseases which accompany or cause it (gall-stones, pancreatic stones, carcinoma, cysts, etc.).

Diagnosis.—This is exceedingly difficult, except when the abdomen, for some reason or another, is opened, and the pancreas can be directly palpated.

A probable diagnosis of chronic interlobular pancreatitis can be made when jaundice occurs associated with dilatation of the gall-bladder but without the emaciation and weakness that develop with carcinoma of the pancreas.

A probable diagnosis of chronic interacinar pancreatitis may be made in patients with diabetes that, at the same time, have cirrhosis of the liver, contracted kidney, or other evidences of arteriolar sclerosis (arterial hypertension, etc.).

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(*d*) *Specific Inflammations of the Pancreas (Tuberculous Pancreatitis; Luetic Pancreatitis)*

Tuberculous pancreatitis is rare, except in the form of (1) *miliary tuberculosis* as a part of general miliary tuberculosis, or (2) *tuberculosis from extension* of neighboring organs (lymph glands, tuberculous kidney).

Syphilitic pancreatitis may occur in congenital syphilis. In acquired syphilis, gumma of the pancreas is rare. A chronic, multilobular cirrhosis of the pancreas, due to syphilis, sometimes occurs and may be accompanied by diabetes.

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2. The Pancreatopathies of Circulatory Origin

Under this caption, brief mention will be made of (1) pancreatic apoplexy, and (2) granular atrophy of the pancreas due to arteriolar sclerosis.

(*a*) *Pancreatic Apoplexy*

In the older literature, pancreatic apoplexy (or hemorrhage into the pancreas) was described as a cause of sudden death in elderly people. Later studies indicate that these were cases of acute hemorrhagic necrosis of the pancreas, at least in the majority of instances.

(*b*) *Granular Atrophy of the Pancreas Due to Arteriolar Sclerosis*

Instances of this condition have usually been included in the bibliography under the head of chronic pancreatitis; in Opie's classification, they would be

designated "chronic interacinar pancreatitis." Hansemann describes a form of chronic pancreatitis that he believes is peculiar to diabetes. He calls it *atrophy of the pancreas* resembling granular atrophy of the kidney, and states that it agrees substantially with what others describe as chronic interacinar pancreatitis. I suspect that these cases are as a rule due to arteriolar sclerosis.

3. The Neoplastic Pancreatopathies

The most important tumor of the pancreas is carcinoma. Adenoma, sarcoma, lymphosarcoma, and angioma are rarely met with. The so-called "proliferation cyst" of the pancreas is probably a multilocular cyst-adenoma—a true tumor.

(*a*) *Carcinoma of the Pancreas*

(*Carcinoma pancreatis; Cancer of the Pancreas*)

Occurrence.—Primary carcinoma of the pancreas is fairly common and of real importance clinically. It involves, as a rule, the head of the gland, but may occupy the whole gland diffusely; it is rarely primary in the body or tail. Secondary cancer occasionally occurs, either as a metastasis, or by extension from neighboring organs.

In a majority of cases primary cancer here is an adenocarcinoma arising from the pancreatic ducts. It is believed by some that a special type has its origin in the islands of Langerhans.

Etiology.—The cause of cancer is entirely unknown. Cancer of the pancreas is about twice as frequent in men as in women. It is a disease of middle or later life, though, rarely, it occurs in children.

Symptoms.—Since cancer of the head of the pancreas is the commonest form, the principal symptoms are (1) *jaundice* (present in three-fourths of the cases and due to compression of the ductus choledochus); this jaundice increases gradually, becoming eventually very intense; it never recedes, and it is associated with enlargement of the gall-bladder; and (2) palpable *tumor* in the epigastrium (observable in about one-fourth of the cases).

Among the other symptoms, epigastric pain (early and constant), anorexia, pancreatic stools, and disturbances of digestion may be present, though any one of them may be absent. The patients usually *emaciate* rapidly, and soon become *cachectic*. Glycosuria occurs in about 25 per cent of the cases. It often disappears before death. As a rule there is no fever.

Diagnosis.—If there be epigastric pain in an elderly person, a palpable tumor in the epigastric region, jaundice, and dilatation of the gall-blad-

der, a positive diagnosis may be made. Unfortunately, such a grouping of symptoms is only occasionally met with.

In the differential diagnosis, we must distinguish cancer of the pancreas from: (1) *gall-stones with jaundice* (gall-bladder contracted, not dilated, onset of jaundice sudden, jaundice often intermittent, absence of emaciation and cachexia, often fever); (2) from *obstructive jaundice due to causes other than gall-stones;* (3) from *chronic pancreatitis* (less emaciation and cachexia, exploratory laparotomy).

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(*b*) *Multilocular Cystadenoma of the Pancreas*

(Proliferation Cyst of the Pancreas)

Though this is in all probability a true tumor, it will be more convenient to refer to it in connection with the other cysts of the pancreas (*q. v.*).

4. Diseases of the Pancreatic Ducts

Under this heading we shall describe (1) pancreatic calculi, (2) ascending inflammation of the pancreatic ducts (sialo-angitis), and (3) cysts of the pancreas.

(*a*) *Pancreatic Calculi*

(Stones in the Pancreatic Ducts; Pancreatic Sialolithiasis)

Definition.—By pancreatic calculus is meant the occurrence of a stone within the ducts of the pancreas.

Occurrence.—Calculi in the pancreatic ducts are rare. In 1,500 autopsies at the Johns Hopkins Hospital, Opie could find only two instances recorded.

Etiology.—In contrast with gall-stones, pancreatic calculi are met with more often in men than in women (5:1). The stones are found most often in people of middle life (30 to 50). The cause of calculus formation is not fully understood, though stasis in the ducts from obstruction and infection of the ducts seem to be important factors, just as in the formation of gall-stones.

Pathology.—The number of stones varies. Solitary calculus is rare; usually, at least several are present, and even hundreds have been found in a single person.

In *size*, the stones vary from that of fine gravel to masses 1½ inches in diameter. In *consistence*, the calculi vary; some are friable; but, as a rule, they are very firm, though they have a nucleus of organic material. In *shape*, they may be irregularly polygonal; sometimes, they take the form of casts of the dilated ducts. In *color*, they are grayish or yellowish white; occasionally, brownish black or black. *Chemically*, they consist chiefly of inorganic salts (calcium carbonate, calcium phosphate, with some sodium phosphate and magnesium phosphate). Stones of different composition have been studied.

The *site* in which the stones are found varies. Usually they are in the larger ducts and cause obstruction. If lodged near the end of the main duct, a stone may compress the ductus choledochus and cause jaundice. Chronic pancreatitis is not infrequently associated with pancreatic calculi. These stones may also cause ulceration and scar formation, or may predispose to an infection and abscess formation.

Symptoms.—In many instances, no symptoms referable to the stones occur during life. When symptoms do occur, they consist of *colicky pain* (especially when calculi are passed), along with *vomiting* and *tachycardia*, and sometimes with *chills* and *fever*, if there be associated infection of the ducts. The stones may be found in the *feces*, and are distinguishable from gall-stones by their chemical composition.

In the cases recognized during life, *diabetes* has been present in about half, but pancreatic lithiasis is rarely a cause of diabetes, probably occurring in not more than one in fifty cases of that disease; moreover, pancreatic calculi may exist for many years without the occurrence of diabetes. There may be *insufficiency of the function of external secretion* of the pancreas in some instances, probably in about 10 per cent. The evidences of this include, bulky stools, steatorrhea and azotorrhea.

Among the *complications* to be feared from pancreatic calculus, we may mention: (1) abscess; (2) ulceration with scar formation or with perforation into the peritoneal cavity or the intestine; (3) the formation of retention cysts (pancreatic ranulae); and (4) chronic indurative pancreatitis.

Diagnosis.—In the cases recognized during life, the diagnosis has, as a rule, been made by finding the stones in the feces. Occasionally, pancreatic calculi have been found unexpectedly, during abdominal operations undertaken for other causes.

It seems probable that x-ray examinations may permit us to recognize more of these cases than formerly, though as yet but little has been done in this direction.

Even when attacks of colic due to sialolithiasis occur, it is hard to distinguish them from attacks of biliary colic; should the pain radiate to the left hypochondrium, or should pancreatic stools, diabetes mellitus, or alimentary glycosuria coexist, the diagnosis of pancreatic calculi would be made probable.

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(*b*) *Inflammation of the Pancreatic Ducts*

(*Ascending Sialo-angitis*)

Etiology.—The condition depends upon bacterial infection following injury to the duct, most often from stone or from direct extension of inflammation from the biliary passages, or through the papilla of Vater from a duodenitis.

Symptoms.—In the *acute* cases, the condition presents no characteristic features; the inflammation may lead to acute hemorrhagic necrosis, or to abscess formation. In the *chronic* cases, the condition may be followed by chronic pancreatitis. The symptoms that accompany inflammation of the pancreatic ducts are, as a rule, due to the disease that causes it (gall-stones, pancreatic calculi, cholangitis), or to its sequelae (different forms of pancreatitis).

(*c*) *Cysts of the Pancreas*

Varieties.—Cysts in the region of the pancreas may be either (1) *true cysts,* lined by epithelium, and derived from the pancreatic ducts or pancreatic acini, or (2) *pseudocysts,* without epithelial lining, and with walls of thick connective tissue.

True cysts may be either (a) *retention cysts,* or so-called *pancreatic ranulae,* or (b) *multilocular proliferation cysts* due to true tumor (*cystadenoma*).

Pseudocysts follow cavity-formation after trauma, or acute hemorrhagic necrosis. They may be situated within the pancreas itself, or they may be bounded partly by the walls of the bursa omentalis.

Pancreatic cysts may occupy any one of three principal *positions* (Körte).

1. Most of them grow directly forward, pushing the stomach upward, and appear under the abdominal wall *between the stomach and the colon transversum.* These cysts are within the cavity of the bursa omentalis, and may be closely simulated by other accumulations of fluid in the lesser peritoneal cavity.

2. Some pancreatic cysts extend above the curvatura minor of the stomach,

and appear *between the stomach and the under surface of the liver* (behind the lesser omentum). In these cases, the pancreas lies above the lesser curvature of the stomach.

3. More rarely, a pancreatic cyst may extend *between the layers of the transverse mesocolon*, especially when the cyst arises in the cauda pancreatis.

The *contents* of these cysts are variable. The fluid may be clear and watery, but it is often viscid, containing mucus. Blood, or its derivatives, is frequently present. Pancreatic ferments may be present in the fluid; it is rare, however, that all three are found, diastase being most often met with. It should be remembered that lipase, diastase, and proteases are sometimes found in the fluids of cysts that are not connected with the pancreas.

Symptoms.—The most important sign is the *tumor* due to the cyst, usually situated between the xiphoid and the umbilicus, causing a rounded protrusion in the middle line or somewhat to the left of it, and varying in size from that of a man's head to a mass largely filling the abdominal cavity. The surface of the mass is smooth; fluctuation can, as a rule, be made out in it, though the tension may be so great that the tumor seems solid. It may, or may not, be movable. The variable position, as regards the stomach, colon and liver, has been referred to above. These cysts sometimes disappear suddenly, owing to *rupture* into the peritoneal cavity or into the intestine; in the latter event, a temporary diarrhea, with whitish fluid, whitish particles, or dark colored masses in the stools, appears. *Pain* of more or less severity usually accompanies pancreatic cyst. *Pressure symptoms* of different kinds may develop (disturbed digestion, jaundice, ascites).

As a rule, there is no marked interference with either the function of external secretion, or that of internal secretion of the pancreas. Opie suggests that the *loss of weight* and *weakness* that accompany pancreatic cysts are due, in part at least, to the digestive disturbances and vomiting caused by pressure.

Diagnosis.—This depends upon the physical signs above described. A history of epigastric trauma, or of a preceding hemorrhagic pancreatitis, may be helpful.

In the differential diagnosis, we must distinguish pancreatic cyst (1) from a *distended gall-bladder;* (2) from a *mesenteric cyst;* (3) from *hydronephrosis;* (4) from *echinococcus cyst of the liver;* (5) from *aneurism of the abdominal aorta;* and (6) from *ovarian cysts.*

The *nature* of the cyst, whether a pancreatic ranula, or a retention cyst due to obstruction of a duct, or multilocular cystadenoma due to true tumor, cannot be recognized before operation; indeed, it is often impossible, even at operation, to be sure of the origin of a cyst in the pancreatic region.

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G. Special Diagnosis of Diseases of the Liver and the Biliary Tract

The diseases of the liver, or the hepatopathies, include:

I. *Hepathopathies of circulatory origin* (chronic passive congestion, acute active congestion).

II. The *degenerative and the infiltrative hepatopathies* (amyloid liver, fatty liver, acute yellow atrophy).

III. The *inflammatory hepatopathies* (abscess, pylephlebitis, the cirrhoses, lues, etc.).

IV. The *parasitic hepatopathies* (echinococcus disease, amebic necrosis).

V. The *neoplastic hepatopathies* (cancer, cyst).

VI. *Abnormalities of the form and position of the liver* (corset liver, Riedel's lobe, hepar mobile).

VII. The *diseases of the biliary passages* (1) cholangitis (catarrhal, infectious); (2) cholecystitis; (3) cholelithiasis; and (4) carcinoma.

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1. Hepatopathies of Circulatory Origin

We distinguish between a *passive* congestion of the liver due to venous stasis, and an *active* congestion of the liver due to an increased supply of arterial blood to the organ.

(*a*) *Chronic Passive Congestion of the Liver*

(Stasis Liver, Passive Hyperemia of the Liver, Cardiac Liver)

Etiology.—The hepatic condition depends upon chronic stasis in the general venous system; it is almost always due to chronic myocardial insufficiency (*q. v.*), though rarely it may be due to obstruction to the vena cava inferior between the right atrium and the hepatic veins.

Symptoms.—*Subjectively,* the patients complain of a feeling of pressure and weight in the upper abdomen; they cannot tolerate tight clothing at the waist, and they find it difficult to take a deep breath. *Objectively,* the liver is enlarged and tender, the margin blunt, the surface smooth. Slight icterus is sometimes present, and often slight dyspeptic disturbance. The spleen may or may not be palpable. Other signs of chronic circulatory insufficiency may coexist (cyanosis, albuminuria, ascites, edema of the legs). The liver may pulsate in tricuspid insufficiency.

If cardiac compensation be restored, the phenomena disappear.

Cases that come to autopsy show a characteristic *nutmeg* appearance (dilatation of central veins, fatty periphery of lobules).

Differential Diagnosis.—Chronic passive congestion of the liver is usually easily recognized clinically, if the patient be studied as a whole. We have to distinguish it (1) from enlargement in *cirrhosis hepatis;* (2) from *pericarditic pseudocirrhosis* (Pick's disease), in which there is obliteration of the pericardium and chronic hyperplastic peritonitis with "icing surface" to the liver; (3) from *cancer of the liver;* (4) from *fatty liver;* and (5) from *amyloid liver.* The condition of the circulation, and the state of the liver itself, will establish the diagnosis, *provided a thorough examination be made.*

(*b*) *Active Congestion of the Liver*

(*Active Hyperemia of the Liver, Tropical Liver*)

Etiology.—Active hyperemia of the liver may follow (1) dietary indiscretions (overeating especially of protein food, abuse of alcohol, coffee and condiments); (2) insufficient bodily exercise; (3) toxic and infectious processes (pyorrhea alveolaris, malaria); or (4) constipation.

It is very common in the tropics, owing to a combination of deleterious influences—climatic, dietetic, general hygienic. Not infrequently a so-called active congestion of the liver is nothing but the early sign of a cirrhosis hepatis, an hepatic abscess, or a carcinoma hepatis.

Symptoms.—Subjectively, there is a sense of fullness and discomfort in the right hypochondrium. The patients say that they are "bilious"; they suffer from disturbances of appetite and constipation, are irritable

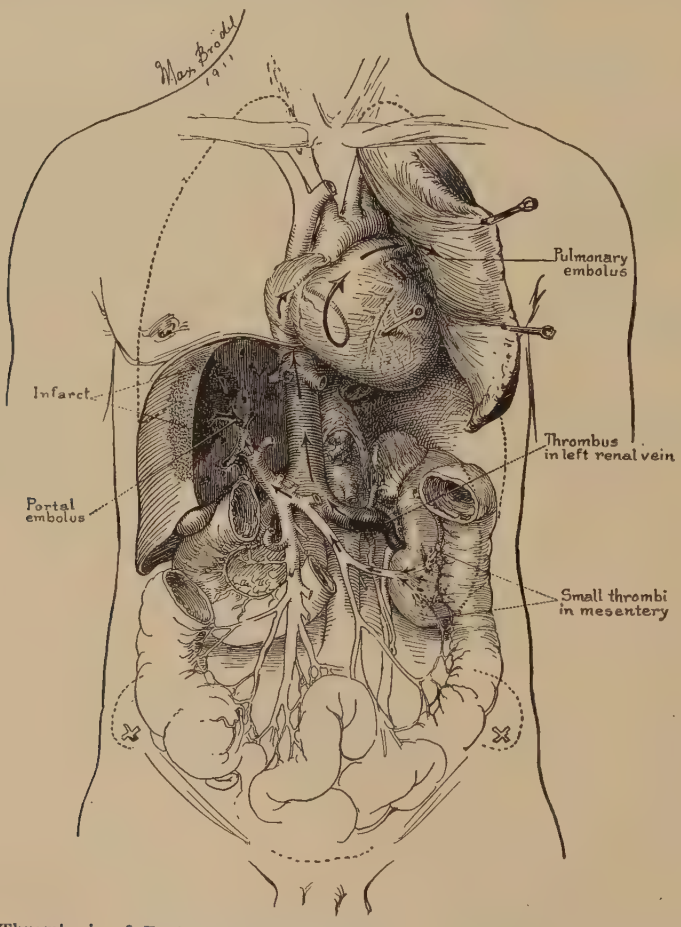

Fig. 421.—Thrombosis of Portal Vessels; Infarction of the Liver. (After M. C. Winternitz; Drawing by Max Brödel; J. H. H. Bull.)

and depressed, often mildly hypochondriacal. Objectively, the liver is slightly enlarged (palpation, percussion), and tender on pressure.

Diagnosis.—The mode of life of the patient, the subjective symptoms and the objective signs usually suffice for the diagnosis. There may be a subicteric tint to the sclera, but Gmelin's test in the urine is negative. The absence of other signs of circulatory insufficiency rules out chronic passive congestion. The coming and going of the local phenomena, and a thorough investigation of the case will safeguard against the overlooking of more serious conditions (cirrhosis, abscess, gall-stones, carcinoma).

(c) *Portal Thrombosis; Pylephlebitis*

Thrombosis of the portal vein may occur in any one of a large series of conditions. It is met with occasionally in connection with thrombosis of the mesenteric veins and now and then in cirrhosis hepatis, in lues hepatis, in chronic proliferative peritonitis, in carcinoma, in cholelithiasis, and in phlebosclerosis. It may be associated with infarction of the liver.

Simple inflammation of the portal vein (pylephlebitis) may be a cause of thrombosis. If suppuration do not occur the thrombus may become organized and a collateral circulation gradually develops. For suppurative pylephlebitis see Abscess of the Liver.

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2. The Degenerative and Infiltrative Hepatopathies

Under this heading we include (1) fatty liver, (2) amyloid liver, (3) acute yellow atrophy, (4) the liver of phosphorus poisoning, (5) the toxic hepatopathy of pyorrhea alveolaris, and (6) atrophic cirrhosis (Laennec); the last mentioned will, however, be described under the chronic inflammations of the liver, though it is primarily a degenerative process.

(*a*) *Fatty Liver*

(*Hepar adiposum*)

Definition.—A condition in which the liver is enlarged, of a yellow color, and contains a great excess of fat, often as much as 30 or 40 per cent by weight, instead of the normal 1 to 5 per cent.

Etiology.—Usually, a fatty liver is due to fatty *infiltration;* this is often a part of general obesity, especially in alcoholics. Sometimes, the infiltration is combined with actual fatty *degeneration,* as in infections, in phosphorus poisoning and in other intoxications (As, Hg, Cu). Degeneration occurs also in tuberculosis, in severe anemias, and, sometimes, in cancerous cachexia.

Symptoms.—There is enlargement of the liver; its margin is rounded, and the surface is smooth, though rather soft. There is no ascites or icterus; and the spleen is not enlarged. In general obesity, it may be very difficult to demonstrate an enlargement of the liver, owing to the marked panniculus adiposus.

(*b*) *Amyloid Liver*

(*Degeneratio amyloidea hepatis, Lardaceous Liver, Waxy Liver*)

Etiology.—Chronic suppurations; lues; usually associated with amyloidosis of other organs (spleen, kidneys, intestines, etc.).

Symptoms.—The liver is large and hard; its margin is rounded; the surface is smooth; the organ is not tender; and there is no jaundice and no ascites. The spleen is enlarged and hard (amyloid); there is usually albuminuria due to amyloid kidney, and often diarrhea due to amyloid intestine.

Diagnosis.—If these symptoms are present, and there is a history of caries of bones, pulmonary phthisis, lues, malaria, ulcers of the legs, or ulcerative neoplasm, the amyloid nature of the hepatic enlargement is tolerably certain.

(c) *Acute Yellow Atrophy of the Liver*

(*Atrophia hepatis acuta flava*)

Etiology.—This form of atrophy may occur suddenly in people apparently healthy, and without known cause, especially in pregnancy, or in the puerperal period. It is sometimes met with at the end of infectious diseases (*e. g.*, typhoid), or in the early stages of lues. It has also been seen in male-fern poisoning. The liver of phosphorus poisoning is an acute toxic degeneration of the liver that must be separated from acute yellow atrophy; in the latter, the liver is chiefly involved, while in phosphorus poisoning, there is a general intoxication involving not only the liver but also the other parenchymatous organs.

The cause of acute yellow atrophy is probably not unitary; intoxications of various sorts (exogenous, enterogenous, etc.) may be responsible. Various bacteria have been described in association with acute yellow atrophy, but none is constantly found. On extraction of the liver with alcohol, fatty acids, that are hemolytic in action, have been obtained.

Symptoms.—At onset, the symptoms resemble those of *gastro-enteritis* and simple *jaundice*. In a few days (8-14), or weeks, very severe symptoms develop; the jaundice becomes more marked, *nausea* and *vomiting* are troublesome, there is *pain* over the liver and in the back, and severe *nervous symptoms* become manifest (headache, dullness, delirium, restlessness, convulsions, coma). There is *splenic tumor;* and *albuminuria*, *cylindruria* and *choluria* are demonstrable. The urine sometimes contains an excess of *amino-acids,* especially leucin and tyrosin crystals (on concentration *in vacuo* to half the original volume, or on precipitation with lead acetate). The ammonia in the urine is likewise increased. The total N of the urine is increased, the urea often diminished. The *stools* are clay-colored, owing to intestinal hypocholia.

The *liver* may, at first, be normal in size, or even slightly enlarged, but, later, it rapidly decreases in volume to half its normal size; the superficial dullness may practically disappear. A *hemorrhagic diathesis* develops (hematemesis, epistaxis, cutaneous ecchymoses, hematuria, metrorrhagia, etc.). In most cases, the disease is fatal.

Diagnosis.—This may be impossible at first, but the diagnosis is easily made later, when the liver begins rapidly to decrease in size, the grave nervous symptoms develop, and leucin and tyrosin appear in the urine. In phosphorus poisoning, amino-acids appear in the urine also, but the anamnesis, or the findings of phosphorus in the vomitus, or in the aspirated gastric contents, will make the nature of the case clear.

(d) *The Liver of Phosphorus Poisoning*

Occurrence.—Formerly, acute phosphorus poisoning was common, owing (1) to the use of phosphorus in the heads of sulphur matches; (2) to the "fashion" of committing suicide by phosphorus poisoning; (3) to the fact that workers in

industries that make use of phosphorus were not adequately protected, owing to the slow development of occupational hygiene. Now, it is unusual to meet with instances of phosphorus poisoning, though they occasionally occur.

Symptoms.—In phosphorus intoxication, the oxidative processes all over the body are inhibited, and widespread fatty degeneration of all the organs (liver, heart, kidneys, nervous system) occurs.

The *liver* enlarges, and becomes tender. There is *jaundice* with bilirubinuria. The *urine* contains albumin and casts, sometimes a trace of sugar, and, often, on concentration, leucin and tyrosin crystals. Working with Abderhalden in 1905, I was able to show the presence of other amino-acids (glycocoll and phenylalanin) in the urine of dogs poisoned by phosphorus. The chlorids of the urine are diminished, the total N increased. There are signs of *acidosis* (increase of NH_3 in the urine). The gas exchange of the body is lessened (diminished oxidation). The *nervous symptoms* at the end are like those of acute yellow atrophy.

Diagnosis.—This depends upon demonstrating that P. poisoning has occurred, either through the anamnesis, or by finding phosphorus in the vomitus or in the aspirated gastric contents. It has a characteristic odor and is phosphorescent in the dark.

(*e*) *The Toxic Hepatopathy Due to Pyorrhea alveolaris*

I have observed a case in which there was marked enlargement and tenderness of the liver in association with a very severe pyorrhea alveolaris with fever. The liver edge was at the level of the umbilicus. The teeth were loose and bathed in pus. Attempts were made at first to clean up the mouth with antiseptic washes but they were of no avail, and large quantities of pus were swallowed by the patient. Finally, an anesthetic was given, and all the teeth were extracted. In a few days the oral sepsis had been overcome, and the temperature fell to normal. The liver, to our surprise, rapidly decreased in size, and a month later the edge was at the costal margin. The general health of the patient rapidly improved.

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3. The Inflammatory Hepatopathies

Inflammation of the liver, or hepatitis, may be acute or chronic. Under *acute hepatitis,* we shall consider (1) Acute (simple) hepatitis. (2) Acute suppurative hepatitis (Abscess of the Liver). Under *chronic hepatitis,* we shall consider the different forms of "cirrhosis" and "pseudocirrhosis" of the liver. In addition, the specific chronic inflammations of the liver must be mentioned, namely *Tuberculosis hepatis* and *Lues hepatis.*

(*a*) *Acute (Simple) Hepatitis*

(Hepatitis acuta simplex; Hepatitis parenchymatosa benigna)

Clinically, we know but little regarding this condition. Probably the toxic hepatopathy due to pyorrhea alveolaris, described above, would be placed here by some authors. Ewald described a clinical picture as "Hepatitis simplex," in which there was swelling of the liver, tenderness in the hepatic region, a subicteric tint to the skin and slight elevation of temperature. Talma (1891) reported cases of "Hepatitis parenchymatosa benigna" in which the same signs were present, and in addition vomiting, diarrhea, jaundice, and enlargement of the spleen—evidently some form of mild, but acute, infectious disease.

In the tropics, many cases of acute hepatitis are reported, the symptoms being more severe than those of "acute active congestion of the liver," already referred to. The attack begins with chill, high fever, swollen and tender liver and pain in the right shoulder. The patients usually recover quickly. There may be recurrent attacks; cirrhosis hepatis or hepatic abscess may occur as sequelae. The whole subject obviously needs elucidation.

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(*b*) *Purulent Hepatitis*

(*Abscess of the Liver; Suppurative Hepatitis; Hepatitis suppurativa*)

Etiology.—Abscess of the liver may follow: (1) *dysentery* (either bacillary or amebic); (2) *suppurative pylephlebitis,* resulting from infected emboli coming through the portal vein (*e. g.,* in appendicitis; in ulcer of the stomach, duodenum, colon or rectum); (3) *extension* of a suppurative cholangitis or pericholangitis

Fig. 422.—Abscess of the Right Lobe of the Liver Forming a Prominent Tumor. (After W. Osler.)

to the liver substance; (4) *pyemia,* especially in ulcerative endocarditis; or (5) *metastasis* from pyogenic infection elsewhere. Any of the pyogenic bacteria may be responsible. In **"amebic abscess"** we have to deal not with a true abscess, but with a necrosis and softening due to ferments manufactured by *Entameba histolytica.*

Symptoms.—Abscess of the liver may exist without causing any pronounced symptoms (*latent abscess*). Often there is *intermittent fever*

(with chills and sweats), and if slight jaundice be present, abscess may be confused with cholangitis accompanying stone in the common bile duct (Charcot's "intermittent fever of hepatic origin"). The *liver* is usually enlarged and tender; occasionally, but only rarely, circumscribed bulging with fluctuation can be made out.

An abscess projecting on the upper surface of the liver sometimes presents a shadow in the *röntgenogram.* With this, there may be dyspnea, dysphagia, and cough, perhaps reflex in origin.

Pains in the hepatic region are usually present, often radiating to the right shoulder. If the abscess approaches the surface, there may be *signs of peritoneal irritation* (vomiting, hiccough, audible friction).

There may be an entire absence of *jaundice.* Usually, the skin has a grayish-green tint; there is often marked *emaciation.* Ascites does not develop. The *spleen* may or may not be enlarged; in some cases it is palpable, in others demonstrably enlarged on percussion.

The *blood* may show a moderate leukocytosis in abscesses due to bacteria, but in amebic necrosis there may be no leukocytosis at all, though a relative eosinophilia may be demonstrable.

Abscess of the liver sometimes *ruptures* into the lung, or pleura, discharging through the bronchi (anchovy-colored pus, and sometimes amebae, in the sputum). Pyopericardium, or subphrenic abscess, may result from perforation of an hepatic abscess. Rupture into the bowel is common. Occasionally, the body wall is perforated, though an abscess pointing on the surface is usually signalled by a boggy swelling and the abscess is opened before it ruptures.

Diagnosis.—Abscess of the liver is more often recognized now than formerly, first, because we are on the lookout for it, especially in patients who have suffered from an illness prone to be followed by hepatic abscess, and secondly, because with blood examinations, röntgenological methods, exploratory puncture, and exploratory laparotomies, we have at our disposal procedures that often give us clews formerly unavailable.

Exploratory puncture of the liver has often been undertaken in doubtful cases. A Record syringe is most convenient. The needle should be 10-15 cm. long, and about as thick as a knitting needle. The little operation should be done under aseptic precautions (see Section III on Exploratory Punctures). It is best to make the puncture under anesthesia as several deep punctures may be required. The needle should be introduced for its whole length, the piston withdrawn slightly to create a vacuum, and the needle then very slowly withdrawn; if the focus of the pus be struck, it will enter the syringe, or even when inspissated a drop or two sufficing for diagnosis will probably be obtained. Favorite sites for puncture are (1) the anterior axillary line in the lowest intercostal space, (2) the mid-axillary line in the 7th space, or (3) over the center of the area of dullness in the back. If pus be not found at the first puncture, the needle should be inserted in several different intercostal spaces and shoved inward at varying angles to the surface. Five or six negative punctures may be followed by success, and

experience has shown that hepatic puncture is usually devoid of danger if suitable precautions are observed.

Since exploratory laparotomy is now so readily undertaken, surgeons have urged that exploratory puncture of the liver be given up and exploratory laparotomy done instead; de Quervain, especially, asserts that, even with a small needle, there is danger of infecting the peritoneum.

In making röntgenograms, the method of teleröntgenography in the direction advised by Köhler (see Examination of the Liver) is valuable.

As Osler has emphasized, in pyemia and in pylephlebitis there are usually multiple abscesses, and they are nearly always fatal even if recognized and treated surgically. The *large solitary abscess,* on the other hand, while serious, often ends in recovery if located in time and thoroughly drained. Amebic abscess (or necrosis) may heal spontaneously if the amebae be killed by injections of emetin hydrochlorid; but some of these abscesses are secondarily infected with pyogenic bacteria and require surgical drainage. When an abscess has develpod in an echinococcus cyst, hooklets may be found in the punctate.

Differential Diagnosis.—We must differentiate abscess and amebic necrosis of the liver (1) from *malaria* (parasites in the blood, leukopenia, therapeutic test with quinin); (2) from *right-sided empyema* (limits of dullness; above all, x-ray examination of thorax); (3) from *subphrenic abscess* (anamnesis, x-ray examination); (4) from *gall-stones with cholangitis causing intermittent fever* (anamnesis, x-ray, surgical exploration); (5) from *echinococcus cyst* (contact with dogs, x-ray, urticaria, complement-fixation test, exploration by laparotomy or puncture and search for fluid containing hooklets); and (6) from *non-parasitic cyst* of the liver.

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(c) *Acute Perihepatitis*

Definition.—An acute inflammation of the peritoneum covering the liver.

Etiology.—This is always secondary, (1) to trauma, or (2) to disease of the liver or adjoining viscera (hepatitis, neoplasm of the liver, ulcer of stomach or duodenum, etc.). Pyogenic bacteria are usually responsible for the inflammation, which may be localized or diffuse, fibrinous, serofibrinous, or purulent.

Symptoms.—These consist of (1) severe pain in the right hypochondrium, increased by movements, including respiration; (2) audible and palpable friction over the liver; and (3) fever, with leukocytosis.

Diagnosis.—If to the symptoms of the primary disease to which the perihepatitis is secondary, pain and tenderness in the right hypochondrium develop, and friction becomes audible and palpable, the diagnosis is clear.

In the differential diagnosis, perihepatitis must be distinguished (1) from *right-sided pleurisy* (absence of primary abdominal disease; local signs higher; no pain on passive movement of the liver).

(d) *Chronic Hepatitis*

Under this heading we shall discuss the diagnosis of (1) *chronic perihepatitis,* and of (2) the different maladies that have been designated *cirrhosis of the liver* (cirrhosis hepatis).

The term "cirrhosis" refers to the tawny color of the liver seen in the ordinary cirrhosis described by Laennec, but it has come to be applied to all forms of chronic inflammation of the liver, irrespective of the color.

Cirrhoses of the liver are roughly divisible into two great groups: (1) portal cirrhosis, in which the injurious agent acting upon the liver is supposed to enter the organ through the portal vein; and (2) biliary cirrhosis, in which the injury to the liver seems to be associated with the radicles of the bile ducts, either through an ascending process, from obstruction or infection below, or through a descending process (biliary excretion).

i. Chronic Hyperplastic Perihepatitis

(Icing Liver; Capsular Cirrhosis of the Liver; General Chronic Perihepatitis; Polyserositis; Polyorrhymenitis; Pericarditic Pseudocirrhosis of the Liver of Pick)

Definition.—Chronic productive inflammation of the capsule of the liver and its peritoneal covering, leading to an appearance resembling

sugar-icing, and often associated with chronic pleuritis and pericarditis, as well as chronic perisplenitis. It is really a part of a general simple chronic peritonitis (*q. v.*).

Etiology.—Sex and age seem unimportant. The cause is not known, though it is believed to be toxic, since several serous membranes may be simultaneously or successively attacked. There is a chronic tuberculous polyserositis, but some cases appear to be wholly independent of tuberculosis.

The lesion may begin in any one of the serous membranes; it may remain localized, or it may gradually involve other serous cavities. It does not involve the organs themselves, but only their serous coverings. It is associated with a serofibrinous exudation, which later may become absorbed, the serous cavity often becoming obliterated by adhesions.

Symptoms.—The disease is exquisitely *chronic*. It may go on unsuspected for years. The patients first notice a sense of *fullness*, or *weight*, in the upper abdomen. Occasionally, there is acute *pain* at onset, and *ascites* develops. As a rule, the pleural and pericardial symptoms follow later on, though, in some cases, pleuritis or pericarditis may precede the perihepatitis.

The ascites is a marked feature and usually necessitates frequent tappings. Most of the cases of often recurring ascites in the bibliography are instances of this disease. The ascitic fluid is of high specific gravity and contains much albumin (over 3 per cent). The general condition may remain good for years. Ultimately, signs of atherosclerosis or of myocardial insufficiency may develop. The subject is further discussed under Chronic Peritonitis.

Diagnosis.—Recurring ascites in a patient who has earlier had an attack of pericarditis, pleuritis, or perihepatitis with transient edema of the legs, is characteristic. The signs of an obliterated pericardial cavity are often present, and Broadbent's sign in the back may be positive.

It must be differentiated (1) from *cirrhosis of the liver* (absence of adherent pericardium, etiology, late appearance of ascites, less frequent tappings); (2) from *lues hepatis* (anamnesis, Wassermann); (3) from *tuberculous peritonitis* (fever, usually less exudate, tuberculosis elsewhere); and (4) from *carcinoma hepatis* (nodular enlargement, rapid course).

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ii. Portal Cirrhosis of the Liver

Under this heading I shall include (1) *ordinary portal cirrhosis* (the so-called *atrophic cirrhosis* of Laennec); (2) *Banti's disease,* or cirrhosis with splenomegaly; (3) the cirrhosis of *hemachromatosis;* and (4) *Wilson's disease,* or cirrhosis of the liver with progressive degeneration of the nucleus lentiformis.

In all forms of portal cirrhosis, chronic degenerative and inflammatory changes occur in the liver, the connective tissue developing about the interlobular or portal spaces, and leading finally to obstruction of the vena porta, with the development of collateral circulations between the vena porta and the superior and inferior caval veins.

I shall describe ordinary portal cirrhosis first, and then briefly mention the less common forms.

1. *Ordinary Portal Cirrhosis of the Liver*

(*Atrophic Cirrhosis (Laennec); Alcoholic Cirrhosis; Gin-Drinker's Liver; Hob-nail Liver*)

Etiology.—The disease begins, as a rule, in *middle life,* usually after forty, and most patients die before the fiftieth year. *Men* are more often affected than women (2:1). Young children are occasionally attacked. *Occupations* that favor alcoholism or the ingestion of highly spiced foods predispose to the disease.

The disease was formerly believed to be almost wholly due to the action of *alcohol* upon the liver; hence the terms "alcoholic cirrhosis" and "gin-drinker's liver." Certainly it is very common in men who use distilled liquors to excess, especially in those who are steady drinkers. More recently, the occurrence of typical cirrhosis in abstainers from alcohol has thrown doubt upon the alcoholic etiology. Clinical experience is, however, very strongly in favor of it for at least many of the cases. Strong alcohol taken on an empty stomach may injure the liver cells directly after absorption, or indirectly through the production of gastro-intestinal catarrh and toxin-production due thereto (fatty acids, enterogenous toxins). The abuse of *highly seasoned foods* is sometimes followed by cirrhosis; hence the terms "dyspeptic cirrhosis" and "non-alcoholic cirrhosis" (Budd). Of late, more stress has been laid upon *intoxications* and *infections* as a cause of cirrhosis hepatis.

Julius Friedenwald, in Welch's laboratory, was able to produce cirrhosis hepatis in rabbits by prolonged intoxication with absolute alcohol. The rabbits grew fat and became ill-tempered at first. Pearce has produced cirrhosis hepatis by injection of hemolytic and hemagglutinative sera, which cause necrotic lesions, the latter

being followed by a reparative interstitial hepatitis and fibrosis. Opie produced experimental cirrhosis by injecting bacteria into the blood after chloroform poisoning.

Pathology.—The *size* of the liver is variable. Often small, it is by no means always so; indeed, it may be enlarged from the beginning, and remain enlarged throughout. If there be much fatty change, the liver is considerably enlarged (*fatty cirrhotic liver*).

In *consistency*, the liver is much firmer than normal and less elastic. The *surface* is granular or hob-nailed, these hob-nails being pale yellowish-brown, or reddish-brown elevations surrounded by grayish-white depressions. The hob-nails are due to islands of hyperplastic liver tissue surrounded by contracted connective tissue bands.

The *histology* of hepatic cirrhosis has been studied by Opie, MacCallum and Kretz (see Text-books of Pathological Histology). The connective tissue change begins in and about the portal spaces, and leads, sooner or later, to *portal obstruction*. This portal obstruction is more or less compensated for by the development of a *collateral circulation* between the portal system of veins and the general caval system. It is this compensatory circulation that accounts for the *hemorrhoids*, the *esophageal varices*, and the *caput medusae* of the clinical picture.

Ascites often develops toward the end, as a result of the portal obstruction, but it must be kept in mind that *tuberculous peritonitis* is a frequent termination in cases of portal cirrhosis.

The *sequence of events* in the disease seems to be (1) a necrosis of the liver cells at the periphery of the hepatic lobules, or in the mid-lobular zone, due to poisoning; (2) hyperplasia of the liver cells remaining; (3) continuing degeneration and regeneration with the persistence of the poisoning; (4) fibrosis with contraction; (5) portal obstruction; and (6) development of collateral circulation.

Symptoms.—The condition is often found unexpectedly at autopsy, having remained latent during life. As a rule, however, patients, sooner or later, present unmistakable symptoms of the disease, due either to the portal obstruction, to the intoxication and the cholemia, or to an accompanying uremia.

In the early stages, the symptoms are those of the accompanying *gastro-intestinal catarrh* that is nearly always present.

The **symptoms of portal obstruction** include (1) *hemorrhoids;* (2) *hematemesis* from esophageal varix; (3) the development of a *collateral circulation* especially visible in the central veins of the abdominal wall; and (4) *ascites.*

The *toxic symptoms* may be mild (itching, weakness, headache, restlessness), or severe (stupor, coma, delirium, convulsive seizures, etc.).

Among the *other symptoms* that may occur are (1) slight *jaundice* at times (in 15 per cent or 20 per cent of the cases); (2) the development of an *hepatic facies* (mud-colored, thin face, with distended venules or nevi); (3) enlargement or contraction of the *liver;* (4) palpable *spleen;* (5) secondary *anemia* without leukocytosis; (6) signs of *functional insufficiency* of the liver (in very advanced cases), including alimentary levulosuria, urobilinuria, and a positive phenoltetrachlorphthalein test.

Diagnosis.—Physicians often fail to recognize beginning cirrhosis, even when it could be easily diagnosed on thorough examination. The disease should be suspected to exist in men who have led irregular lives, and especially in those addicted to alcoholism. If such persons suffer from symptoms of indigestion, and the liver be found enlarged and tender, a beginning cirrhosis is probable. If there be also enlargement of the spleen, pain in the right hypochondrium, and a subicteroid tint to the skin and sclera, cirrhosis hepatis is almost certain. Of course, after the signs of portal obstruction have developed, the diagnosis becomes easier.

In advanced cases, the hepatic facies may give a clew at once to the diagnosis of cirrhosis. The functional tests for hepatic insufficiency are unfortunately of no use in making an early diagnosis; they may even be negative with advanced cirrhotic change. In the **differential diagnosis,** we must distinguish portal cirrhosis (1) from *biliary cirrhosis* (age, persistent jaundice, larger spleen, extreme chronicity, absence of signs of portal obstruction); (2) from *other enlargements of the liver* (chronic passive congestion, fatty liver, amyloid liver, leukemic liver, lues hepatis, carcinoma hepatis); (3) when there is hematemesis, from *gastric ulcer, duodenal ulcer* and *carcinoma ventriculi* (anamnesis, examination of gastric contents, x-ray examination); (4) after ascites has developed, from *other causes of ascites* (polyserositis, myocardial insufficiency, cachexias, tuberculous peritonitis, carcinoma peritonei, thrombosis of the portal vein).

In the differentiation of the *different forms* of portal cirrhosis from one another, we distinguish the ordinary type (Laennec) from (5) *cirrhosis of hemachromatosis* (bronzed skin, diabetes); (6) from *Banti's disease* (severe anemia, primary enlargement of the spleen, youth); and (7) from *Wilson's disease* (*q. v.*).

2. *Portal Cirrhosis of the Liver with Primary Splenomegaly (Banti's Disease)*

This affection has been described in Part VII, Diseases of the Blood (*q. v.*).

3. *Portal Cirrhosis of the Liver Associated with Hemochromatosis (Bronzed Diabetes; Diabète bronzé; Siderogenous Hemolysis)*

Definition.—A rare disease, occurring chiefly in men of middle age, and characterized by hemolysis, with accumulation of pigment in the liver, pancreas and skin, followed by chronic hepatitis and chronic pancreatitis, the latter sometimes resulting in destruction of sufficient islands of Langerhans to cause diabetes mellitus.

Etiology.—The cause of the hemolysis is unknown, though many cases have been studied carefully in the pigmented stage. The cases have been collected and analyzed by Futcher, and by Potter and Milne.

Symptoms.—The disease begins with disturbances of digestion, pain in the right hypochondrium, and weakness. The skin becomes pigmented, the liver enlarged, and the spleen palpable. In the later stages, glycosuria appears. The patient may have any of the symptoms of portal cirrhosis (*q. v.*), or of diabetes mellitus (*q. v.*).

Diagnosis.—In outspoken cases, with typical pigmentation, enlargement of the liver and spleen, and glycosuria, the diagnosis is easy. In the differential diagnosis, we must distinguish the cutaneous pigmentation of hemochromatosis (1) from that of *Addison's disease* (spleen and liver not enlarged, no glycosuria, pigmentation of the mouth, histological examination of the skin); (2) from that of *argyria* (color, histology); (3) from that of *chronic jaundice* (scleral icterus); and (4) from that of *ochronosis* (localization in cartilage, alkaptonuria).

4. *Portal Cirrhosis of the Liver with Progressive Degeneration of the Nucleus lentiformis (Wilson's Disease; Westphal's Cerebral Pseudosclerosis)*

This disease is taken up in the section dealing with diseases of the nervous system (see Part XII, Subdivision II).

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iii. The Biliary Cirrhoses of the Liver

Definition.—By biliary cirrhosis of the liver is meant a chronic hepatopathy characterized, *anatomically,* by inflammation of the radicles of the bile vessels and increase of connective tissue, and, *clinically,* by persistent chronic jaundice and marked enlargement of both liver and spleen.

Varieties.—Two main forms are distinguished: (1) the hypertrophic biliary cirrhosis of Hanot; and (2) the obstructive biliary cirrhosis of Charcot. In both cases, a pericholangitic fibrosis follows the radicular cholangitis.

1. *The Hypertrophic Biliary Cirrhosis*

(*Hanot's Disease; Hypertrophy of the Liver Associated with Fibrosis*)

Symptoms.—This rare disease begins with discomfort in the hepatic region, disturbances of digestion, and mild jaundice. Gradually, the jaundice increases and becomes persistent. The liver and spleen gradually enlarge, and distend the upper abdomen; hence the French description *"cirrhose avec ictère sans ascite."* Signs of portal obstruction do not appear. A hemorrhagic diathesis may develop (epistaxis, cutaneous petechiae). There is polyuria, bilirubinuria, and urobilinuria, but bile is present in the stools. Febrile attacks, without apparent cause, are common.

The disease is exquisitely chronic, the patients remaining very well for many years. Ultimately, there is emaciation and weakness. The skin becomes dry, and sometimes a lenticular exanthem, especially on the chin, forehead and palms of the hands, appears. Signs of cholemia may develop

and the intoxication may prove fatal; otherwise, the patients die from myocardial insufficiency, or from general cachexia.

In children, the spleen may be larger than the liver; this is the *juvenile type* of splenomegalic biliary cirrhosis, described by Gilbert and Fournier. Such children are often stunted in their growth and show a delayed puberty, evidence of involvement of the endocrine functions. Some of the patients have hippocratic fingers.

Diagnosis.—The insidious development, in young persons (not alcoholic), of marked enlargement of the liver and spleen, a chronic progressive jaundice, and periodic attacks of abdominal pain, with fever and leukocytosis, is highly suggestive of this rare condition, especially if there be signs neither of cholelithiasis nor of portal obstruction present.

Hanot's cirrhosis must be differentiated (1) from *portal cirrhosis* (age, etiology, signs of portal obstruction, less jaundice, constipation rather than diarrhea, shorter course); (2) from *other enlargements of the liver;* and (3) from *other causes of chronic jaundice* (gall-stones, neoplasm, syphilis).

2. *The Obstructive Biliary Cirrhosis (Charcot)*

Etiology.—The radicular cholangitis in this form of biliary cirrhosis is due to mechanical obstruction, especially of the ductus choledochus, by gall-stones, neoplasm, compression, or adhesions.

Symptoms.—This form of cirrhosis hepatis takes a rapid course, rarely lasting more than a year or two. There is severe jaundice, with pronounced symptoms of cholemia or hepatargia. The spleen and liver are enlarged, and ascites may develop. In the latter respect, and in the absence of bile from the stools, this form differs from Hanot's disease.

Diagnosis.—The diagnosis depends upon (1) a discovery of the cause of the biliary obstruction; (2) the rapidity of the course; (3) the intensity of the jaundice in association with intestinal acholia; (4) the absence of a very large splenic tumor, and (5) the presence of ascites.

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(e) *The Hepatopathies of Specific Inflammatory Origin*

Under this heading must be included (1) lues hepatis; and (2) tuberculosis hepatis.

i. Lues hepatis

(*Syphilis of the Liver*)

In *congenital syphilis,* the liver may be found diseased at birth, or the signs of involvement may come out during childhood, or even later (*syphilis hereditaria tarda*). There is moderate enlargement of the liver, with tenderness, and symptoms of indigestion. Sometimes there is ascites and

Fig. 423.—Syphilitic Liver Showing Extreme Irregularity, the So-called "Botryoid" Liver. (After W. Osler.)

enlargement of the spleen. Other signs of congenital lues are present, and the Wassermann reaction is positive.

In *acquired syphilis,* the liver may be involved, either during the secondary period (interstitial hepatitis causing enlargement with icterus), or in the tertiary period (gumma). The coarse multilobular form of cirrhosis of the liver is often due to syphilis.

An important sign in the diagnosis of acquired syphilis of the liver is

an audible friction sound over the liver, due to perihepatitis. Sometimes the friction rub is palpable. The elder Janeway was accustomed to lay great stress upon this diagnostic sign. The friction is perceptible only when the abdominal walls are relaxed, and the non-ascitic patient is not too fat. As a rule, ascites develops only late in the chronic hepatitis due to syphilis.

The age of the patient, the anamnesis, and the Wassermann reaction are important for diagnosis.

A therapeutic test is always useful, since iodid of potassium usually causes rapid improvement unless the disease has gone on to the stage of syphilitic cirrhosis (coarse multilobular cirrhosis).

Fever is a common accompaniment of lues hepatis. I remember one instance of a physician, in whom fever had continued for months. Lues had not been suspected. A Wassermann test was made as a routine and found positive. Under salvarsan and iodid of potassium the symptoms rapidly cleared up, the fever disappearing entirely in a few days.

ii. Tuberculosis hepatis

Several forms of tuberculosis of the liver occur. *Miliary tuberculosis* of the liver may occur as a part of a general acute miliary tuberculosis. The liver may be involved in a tuberculous process arising either from *extension of tuberculous disease from a neighboring organ* (kidney, lymph gland), or by *metastatic deposit* of tubercle bacilli in the hepatic vessels.

The condition is relatively rare, and is but seldom recognized during life.

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4. The Parasitic Hepatopathies

Amebic necrosis has already been described in connection with abscess of the liver. Here we have still to consider echinococcus disease of the liver.

(*a*) *Echinococcus of the Liver*

(*Hepatic Echinococcus, Hydatids of the Liver*)

Etiology.—(See Description of the Worm in Section VIII.)

Forms.—Hydatids of the liver may develop either as (1) echinococcus cysticus, or as (2) echinococcus multilocularis.

i. Echinococcus cysticus

(*Echinococcus unilocularis*)

Occurrence.—The cyst develops in the liver and causes changes in the form of the organ and in its tissues. The *size* may vary from a small sac to a huge mass filling up most of the abdomen.

The parenchyma of the liver may atrophy from pressure, and the bile ducts may also be compressed by the tumor. In rare cases, the cyst may project into the thorax, the diaphragm sometimes being shoved up as high as the second rib.

The sac may *perforate* into the right pleural cavity, the right lung, the pericardial sac, or the peritoneal cavity; sometimes it breaks through the abdominal or the thoracic wall; finally, it may rupture into the stomach, the intestine, the biliary passages, or the vena cava. The most common site of rupture is, however, upward into the thorax, with development of a purulent pleuritis, often fatal.

Symptoms.—The symptoms before rupture are due chiefly to the size and the position of the cyst. With a small cyst, there may be no symptoms whatever. When the cyst is larger, it causes general or local enlargement of the liver. Sometimes a cyst is palpable, and then fluctuation may be felt, and a peculiar thrill (hydatid thrill) may be demonstrable. The fluid in the cyst may be under such tension that the mass feels like a solid tumor. If the portal vein be compressed, signs of portal obstruction appear. If the bile passages are pressed upon, there is jaundice.

Subjectively, the cyst is not painful, though, when large, there is a feeling of heaviness, and of tension, in the region of the liver. Sometimes,

suppuration sets in about a cyst, and the clinical picture of hepatic abscess develops.

In case of *perforation,* there is usually severe pain. The other symptoms depend upon the organ into which the cyst ruptures. It has long been known that urticaria may follow rupture of a hydatid cyst, or even the aspiration of a cyst.

Diagnosis.—The presence of an irregular, painless mass, especially in the left lobe of the liver, or the presence of a large fluctuating tumor in the epigastrium yielding a hydatid thrill, points to echinococcus. The complement-fixation test will be helpful, if the condition be suspected. An eosinophilia may point to invasion by an animal parasite. Thus far, x-ray examinations have not been especially helpful in the diagnosis of echinococcus of the liver, but a case has been reported in which a röntgenogram was of aid.

In the **differential diagnosis,** we must distinguish echinococcus of the liver (1) from *carcinoma hepatis;* (2) from *lues hepatis;* (3) from *abscess of the liver* (one may develop when a cyst suppurates); (4) from *hydronephrosis;* (5) from *subphrenic abscess;* and (6) from *right-sided empyema.*

ii. Echinococcus multilocularis

(*Multilocular echinococcus, Echinococcus alveolaris*)

Occurrence.—In this form, the daughter cysts come to exogenous development, and one cyst is attached to another, the daughter cysts often appearing as though pinched off from the mother cyst. These cysts lie close together, and have been compared in structure to the appearance of a honeycomb. The capsule becomes thickened and as hard as cartilage, and is often adherent to its surroundings. It may be that this form of echinococcus belongs to a different species than the ordinary echinococcus cyst, though this is not yet certain.

Clinically, the *mass* in the liver feels firm and nodular, and is tender on pressure. Hydatid *thrill* and *fluctuation* are absent; *jaundice* is usually present, and there is rapid *emaciation* and loss of strength.

This form of hydatid of the liver is often mistaken either for carcinoma hepatis, or for hypertrophic cirrhosis. The disease may last several years; but it usually terminates fatally, in the long run, after a period of cachexia, edema, exhausting diarrhea and cholemic phenomena.

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5. The Neoplastic Hepatopathies

(*Tumors of the Liver*)

The commonest neoplasm of the liver is *carcinoma* (rarely primary, often secondary). *Sarcoma* of the liver occurs, but is very rare; it, also, may be either primary or secondary. *Adenoma, cystadenoma, hypernephroma* from aberrant adrenal, and other forms of hepatic tumor may be met with occasionally. An interesting condition is the *cystic disease of the liver* that occurs in association with congenital cystic kidneys.

(*a*) *Cancer of the Liver*

(*Carcinoma hepatis*)

Varieties.—*Primary* carcinoma of the liver is very rare; it may occur as a nodular, multiple cancer (65 per cent), as massive carcinoma (23 per cent), or as infiltrating, or diffuse, carcinoma (12 per cent); in the latter instance, it may be mistaken, at autopsy, for portal cirrhosis.

Secondary carcinoma is a very common disease, following carcinoma of the digestive tract. Larger or smaller nodules are scattered through the liver, those that reach the surface forming definite bosses, which are sometimes umbilicated and often palpable.

Symptoms.—The onset is insidious, with failure of the general health, loss of weight, and the gradual development of a cachexia. In at least one-third of the cases, the condition is recognized only at autopsy. In some instances, signs due to the primary growth in other organs (stomach, colon, rectum) may be demonstrable.

The symptoms due to the hepatic growth itself consist of *pain* in the region of the liver, *enlargement* of that organ, *jaundice,* and ascites.

Jaundice is present in somewhat more than 50 per cent of the cases. Ascites is rather less common. Both ascites and jaundice are present in about one-fifth of the cases.

Recognition depends mainly upon the progressive enlargement of the liver, and one may be certain if umbilicated bosses are palpable. The spleen is not enlarged unless thrombosis of the portal vein or cirrhosis hepatis complicate the cancer.

Diagnosis.—Rapid enlargement of the liver, especially if it be nodular, in a person at middle life or later, associated with jaundice and the development of a cachexia, is characteristic.

It is sometimes difficult to be sure that the liver contains a neoplasm. Tumors of adjacent organs may be mistaken for tumors of the liver, and other causes of enlargement of the liver may be taken to be cancer (*e. g.*, cirrhosis, abscess, lues, or echinococcus cyst).

If a neoplasm be certainly present in the liver, the chances are strongly in favor of its being cancer, and they are 30 or 40 to 1 that the carcinoma is secondary, not primary.

In the **differential diagnosis,** we must be especially on our guard to differentiate cancer of the liver (1) from *abscess of the liver* (etiology, absence of cachexia, jaundice and ascites less common, fever and leukocytosis more marked); (2) from *lues hepatis* (more painful, anamnesis, positive Wassermann, therapeutic test); (3) from *portal cirrhosis* (etiology, absence of bosses, signs of portal obstruction); (4) from *biliary cirrhosis* (youth, early jaundice, smooth surface of liver, splenomegaly, chronicity); (5) from *hydatid disease* (smooth tumor, splenic enlargement, chronicity, etiology, thrill, complement-fixation test).

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6. Abnormalities in the Form and Position of the Liver

Under this heading we shall include (1) corset-liver; (2) Riedel's lobe; and (3) movable liver.

(*a*) *Corset-liver*

Occurrence.—The liver may become constricted by the corset (in women), or by a tight belt or strap (in men). The constriction leads to atrophy from pressure, followed by fibrous change. Such livers may be seen during laparotomy; much more often at autopsy. One or more furrows are visible, due either directly to the external pressure, or, indirectly, to pressure of the ribs, or to bands of the diaphragm.

Diagnosis.—The condition may be suspected during life in women who practice tight lacing. Symptoms of indigestion may be present.

(*b*) *Riedel's Lobe*

The anterior margin of the right lobe of the liver may be elongated so as to form a tonguelike projection, spoken of as *linguiform lobulation*, or *Riedel's lobe.*

This is a *partial hepatoptosis*, associated with gall-stones, cholecystitis, and enlargement of the gall-bladder. Tight lacing is sometimes a factor if it cause kinking of the cystic duct and dilatation of the gall-bladder. The lobule is very freely movable. Sometimes it is painful, and tender on pressure. The resistance of such a portion of the liver to disease seems to be lowered, for gumma, abscess or tumor not infrequently develops in a linguiform lobule.

Diagnosis.—The lobule can often be felt on abdominal palpation, continuous with, and moving with, the liver. A Riedel's lobe is of clinical importance, since it is sometimes mistaken for a floating kidney, a hydronephrosis, a dilated gall-bladder, or a tumor of the stomach, intestine, omentum, pancreas, or ovary.

(*c*) *Mobile Liver*

(Movable Liver, Wandering Liver, Hepar mobile, Hepatoptosis, Hepar ambulans)

Occurrence.—A mobile liver is usually a part of a general splanchnoptosis. It occurs most often in women with relaxed abdominal walls.

Symptoms.—The liver may be felt as a large movable tumor in the right upper abdomen; on standing, it may sink low in the abdomen, often as far as the symphysis, but in the recumbent position it can be shoved back into its normal place. Often the incisures of the liver can be distinctly felt, and, in some cases, one can grasp the whole organ in the two hands. Rarely, such a movable liver becomes adherent at an abnormal site. All transitions occur between the normal fixation of the liver and a wandering liver of the extreme type above described.

The subjective symptoms due to movable liver vary extremely. Sometimes there are no symptoms whatever complained of. Other patients have disturbances of digestion and a feeling of weight and tension in the abdomen. Occasionally, kinking of the portal vein or of the vena cava may cause venous obstruction.

Diagnosis.—If the liver be freely movable and easily replaceable, there should be no difficulty in making the diagnosis, though the first time one meets with a wandering liver, the surprise is great. When such a liver becomes adherent, the diagnosis may indeed be difficult, and the condition has been confused with omental tumor, movable kidney, hydronephrosis, and even pelvic tumor.

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H. Special Diagnosis of Diseases of the Bile Ducts and of the Gall-bladder

1. Inflammation of the Bile Vessels

Occurrence.—Inflammation of the bile ducts (*cholangitis*) and of the gall-bladder (*cholecystitis*), due to infections, are very common. These inflammations may be *acute, subacute,* or *chronic;* they may be *slight* or *severe;* and, in form, they may be *catarrhal, purulent, pseudomembranous* or *gangrenous.*

A catarrh of the gall-bladder is the commonest forerunner of gall-stones (*cholelithiasis*). Typhoid bacilli, and colon bacilli, are the common agents of infection of the biliary tract. They gain entrance, chiefly by way of the portal circulation and excretion into the bile (*descending infection*), partly by way of

the papilla duodeni into the ductus choledochus (*ascending infection*); infection may occasionally occur also by way of the general circulation, by way of the lymphatics, or by direct extension from the peritoneal covering.

Congenital hemolytic jaundice has been described in Part VII.

(*a*) *Simple Catarrhal Jaundice*

(*Icterus catarrhalis, Acute Catarrhal Cholangitis*)

Etiology.—This is most often due to a catarrhal inflammation of the orifice of the ductus choledochus, resulting in swelling of the mucous membrane, and blocking of the orifice of the papilla duodeni with mucus, an obstruction that causes jaundice. It is *usually secondary to acute gastroduodenal catarrh*, which, in turn, follows dietetic errors, exposure to cold, or, perhaps, violent emotion. Sometimes the obstruction may be due to hyperplasia of the lymphoid tissue at the lower end of the ductus choledochus (Eppinger). It is likely that some cases of catarrhal jaundice in acute infectious processes are due to a descending infection of the ducts.

Symptoms.—After a *digestive disturbance* (anorexia, nausea, perhaps vomiting, or diarrhea), *jaundice* of the sclera, the skin, and the mucous membranes insidiously develops and gradually increases in intensity. The *urine* is dark brown or black, and on shaking shows a yellow foam; it usually contains a little albumin and a few casts; Gmelin's test for bile pigment is positive, sometimes, before the sclerae turn yellow. *Constipation* sets in, with clay-colored, foul stools (*intestinal acholia* or *hypocholia*). The *liver* may or may not be slightly enlarged and tender; if it and the gall-bladder become palpable and tender, the possibility of a cholecystitis, or of an extension of the cholangitis to the intrahepatic radicles, should be thought of. Other symptoms are bradycardia, pruritus, weakness, headache, and depression—mild symptoms of *cholemia*.

The symptoms usually disappear in from two to four weeks, though an attack may last six weeks or even longer. If it persist, the suspicion of a mistaken diagnosis is aroused (acute yellow atrophy, cancer, gall-stones, chronic indurative pancreatitis).

Diagnosis.—Occurring in a young person, after a definite attack of gastro-intestinal catarrh, without pain, running a mild course, with subsidence of the symptoms within a month, the diagnosis is clear.

In the differential diagnosis, we must distinguish simple catarrhal jaundice (1) from obstructive jaundice due to *impaction of a gall-stone* (history, pains earlier, fever, chills and sweats); (2) from *Weil's disease* (acute onset, fever, splenic enlargement); (3) from *acute yellow atrophy* (failure to clear up, advent of grave cholemic symptoms, rapid diminution in size of liver, amino-acids in the urine); and (4) from *carcinoma* compressing the ductus choledochus (age, duration beyond six weeks, emaciation and cachexia).

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(*b*) *Epidemic Catarrhal Jaundice*

(Infectious Jaundice; Icterus infectiosus; Weil's Disease)

Definition.—A disease that occurs in small or large epidemics, usually in the summer, beginning as a gastro-intestinal catarrh with fever and followed by jaundice, due to catarrhal cholangitis, enlargement of the spleen, and albuminuria.

Etiology.—The disease is obviously an infection, and probably follows the ingestion of contaminated foods. The *Bacillus paratyphosus* and the *Bacillus proteus vulgaris* seem to be the commonest causative agents. Recently, Japanese observers have discovered that Weil's disease is due to a *Spirochaete* infection.

The disease is relatively common in the Southern United States. In 1899-1900, there was a large outbreak in North Carolina. In the Baltimore jail, Dr. F. J. Sladen and I through the courtesy of Dr. Wilkins, physician to the jail, studied a small epidemic. The patients recover as a rule, though in the severer forms there may be fatalities. Osler reports a fatal case in the North Carolina epidemic.

Symptoms.—The onset is sudden, with high fever; in a few days, there is severe prostration, jaundice (slight or severe), splenic tumor, and albuminuria. In the second week, the fever falls by "stair-case" descent, and the symptoms clear up. There is a tendency to a mild relapse after a remission of a week. In the cases reported by Weil (1886), the cases occurred in groups and were especially common among butchers. Osler suggests that ordinary acute catarrhal jaundice may represent the sporadic form of the disease.

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(c) *Purulent Cholangitis*

(Cholangitis purulenta; Cholangitis suppurativa)

Definition.—A purulent inflammation of the bile ducts.

Etiology.—The disease is due to *infection* with pyogenic bacteria (*Bacillus coli, Bacillus typhosus, Streptococcus pyogenes, Staphylococcus aureus, Pneumococcus*), arriving in the bile ducts either by way of the circulation (*descending infection*), or by way of the papilla duodeni from the duodenum (*ascending infection*). It is nearly always associated with cholecystitis, and it rarely occurs independent of injury to the ducts from either gall-stones or compressing neoplasms, though occasionally it may follow directly upon some infection like typhoid fever or pneumonia.

Symptoms.—The symptoms of the purulent cholangitis are preceded by the symptoms of the primary disorders on which it depends, namely, those of gall-stones, of malignant disease, or of a general or local infection.

As the purulent cholangitis develops, *jaundice,* if not already present, appears, along with *fever, chills and sweats.* There are remissions and exacerbations of the symptoms. *Pain* may be absent or present; if present, it may be slight or severe. The *liver* is enlarged and tender; if cholecystitis coexist, the gall-bladder is tender and enlarged. The *spleen* is usually palpable. There is an outspoken polymorphonuclear *leukocytosis.*

Multiple abscesses may develop in the liver. Metastatic infections or pyemia may occur. Extension to the peritoneum is another possible complication; a subphrenic abscess may develop, or a fistulous communication with the duodenum, colon, pleura or lung may be formed.

Diagnosis.—Fever, chills, sweats, and a leukocytosis, with jaundice, pain, and enlargement of the liver and spleen point to purulent cholangitis. Malaria is easily ruled out (parasites, leukopenia). In the differential diagnosis, we have to distinguish the disease (1) from *hepatic abscess,* and (2) from *suppurative pylephlebitis.*

(*d*) *Chronic Cholangitis*

Etiology.—A chronic catarrh often involves the whole biliary tract (ductus choledochus, ductus hepaticus, ductus biliferi, ductus cysticus, and vesica fellea). According as it is, or is not, associated with gall-stones, a calculous, and a non-calculous form are distinguished. It is due to a low grade infection with bacteria that are but mildly pathogenic.

There is chronic hyperemia, thickening of the walls of the biliary passages, with partial obstruction of the lumen, and often dilatation. The character of the bile changes; it may consist of colorless mucus.

Symptoms.—The clinical picture is that of a chronic intermittent jaundice; should the obstruction become complete, the jaundice is persistent. There may be little or no fever, except in exacerbations. Gall-stone colic may complicate the picture in the calculous form.

Diagnosis.—The condition must be differentiated (1) from *carcinoma* compressing the ductus choledochus (emaciation, cachexia, signs of primary growth), and (2) from *hypertrophic biliary cirrhosis* (marked enlargement of liver and spleen, youth).

(*e*) *Acute Cholecystitis*

(*Acute Inflammation of the Gall-bladder; Cholecystitis acuta*)

Etiology.—The disease is usually a part of a general cholangitis, but the gall-bladder may be infected to a large degree independently of the rest of the biliary tract. The real cause is always bacterial infection, the infectious agents reaching the gall-bladder usually by way of the circulation, occasionally from the ductus choledochus through ascending infection. The Bacillus coli, the pyogenic cocci, and the Bacillus typhi abdominalis are the bacteria most often concerned. Perhaps the most important of these is the typhoid bacillus. Welch and Blackstein showed years ago that, on injection of typhoid bacilli into rabbits, these bacilli appear in the bile and may remain living in the gall-bladder for a long period. Acute cholecystitis is a common complication of typhoid fever, and, even in the cases presenting no symptoms of acute inflammation of the gall-bladder, it is probable that typhoid bacilli are practically always present in the bile during the course of typhoid fever; indeed, infection of the gall-bladder is the most common origin of the so-called typhoid bacillus-carrier. Typhoid bacilli in the gall-bladder often keep up a mild catarrhal cholecystitis and are perhaps the most frequent cause of gall-stones.

In this connection, the writer's personal experience may be of interest. At the age of eight, he had an attack of typhoid fever; thirty-five years later, at the

age of forty-three, he was operated upon by Dr. Finney and four rather large gall-stones and a chronically inflamed appendix were removed. The bile was sterile, but from the center of one of the gall-stones, Dr. Austrian was able to grow the typhoid bacillus in pure culture.

Conditions that lower the vitality of the wall of the gall-bladder, and conditions that interfere with the outflow of bile, are contributing factors in the etiology of cholecystitis.

Symptoms.—The symptoms vary according to the nature of the inflammation, which may be catarrhal, purulent, phlegmonous, gangrenous, or membranous.

In the mild catarrhal infections, there may be no symptoms noticed by the patient, or they are so slight as to be considered symptoms of transient indigestions. In severer cases, there is pain and tenderness in the region of the gall-bladder, rigidity of the right upper rectus, nausea, and vomiting; a little later, the enlarged and tender gall-bladder can sometimes be palpated. The tumor, due to the distended gall-bladder, is pyriform, moves with respiration, and, if not adherent, can be displaced by the palpating hand. Jaundice does not occur unless there is an associated cholangitis, or impaction of a gall-stone in the hepatic or the common duct. The polymorphonuclear neutrophils are increased in the blood (12,000-20,000).

In most cases, the course is brief, the acute symptoms subsiding within a week or two. Unfortunately, there is a strong tendency for the disease to become chronic, in which event gall-stones often form, though not always.

Complications.—Among these, there may occur (1) *blocking of cystic duct* (hydrops, or empyema, of the gall-bladder); (2) *blocking of the ductus choledochus* (chronic jaundice; if cholangitis also, then chills, fever and sweats); (3) *perforation* of the gall-bladder or duct, with rupture into the peritoneal cavity (general peritonitis, subphrenic abscess), or into the intestine (ileus); (4) *purulent hepatitis* and *general sepsis;* (5) *pericholecystitis* with adhesions to the pylorus and duodenum (gastrectasia); (6) *cancer* of the gall-bladder.

Diagnosis.—This is easy when the typical symptoms, described above, are present. In the *latent* cases, diagnosis may be difficult; and in the *fulminating* cases, with perforation or gangrene, other causes of severe symptoms in the right upper quadrant may be hard to rule out. Confusion of acute cholecystitis with acute appendicitis often occurs, due either to a low situation of the gall-bladder or to a high situation of the appendix.

In the differential diagnosis, we must distinguish acute cholecystitis (1) from *acute appendicitis* (pain more localized at the beginning, Head's zone, previous history, careful consideration of palpatory signs); (2) from *acute peritonitis due to perforation of a gastric or duodenal ulcer.*

(*f*) *Chronic Cholecystitis*

(Chronic Inflammation of the Gall-bladder; Cholecystitis chronica)

Etiology.—A cholecystitis may be chronic from the beginning; more often, it follows an acute attack. It is apparently always due to a chronic infection with bacteria of low virulence, and is usually associated with general catarrh of the biliary tract and with gall-stones. There is a definite group of cases, however, in which gall-stones are absent (non-calculous cholecystitis).

Fig. 424.—Cholecystitis chronica with a Stone in the Cystic Duct. (After W. C. MacCarty, "Collected Papers by the Staff of St. Mary's Hospital, Mayo Clinic," published by W. B. Saunders Co., Phila.)

Symptoms.—The symptoms are practically the same as in gall-stones (*q. v.*). It is almost impossible to be sure whether or not gall-stones are present, though an x-ray examination may sometimes reveal them. Indeed, the symptoms of gall-stones are largely dependent upon the accompanying cholecystitis.

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(*g*) *Gall-stones*

(*Cholelithiasis; Biliary Calculus*)

Definition.—Gall-stones are calculi that form in the biliary tract, most often in the gall-bladder, though sometimes in the ducts, especially in the hepatic duct.

Occurrence.—At autopsy, 5 or 10 per cent of all human beings examined have gall-stones. As regards *age,* at least 75 per cent of the positive cases at autopsy are in persons over forty. In less than 1 per cent, the age is below twenty. Many gall-stones are, however, formed before forty, so that the autopsy records are, in this respect, somewhat misleading. It is probable that gall-stones form soon after an attack of typhoid fever or other catarrhal infection of the biliary tract.

Gall-stones are far more common in *women* than in men, probably

from 2 to 5 times as frequent. This may be due to the more sedentary habits of women, though the influence of tight lacing, of repeated pregnancies, and of puerperal infections may be partly responsible.

Catarrhal cholecystitis, due to bacteria, practically always precedes the formation of gall-stones.

Among the *predisposing factors,* besides those mentioned, are chronic cardiac disease, pulmonary disease, chronic diseases of the digestive tract, dietary indiscretions, and the abuse of alcohol. Gall-stones are only about half as common in Japan as in Europe and America (Miyake).

Number, Size, Shape and Position.—There may be a single gall-stone, a few stones, or several thousand. The greater the number, the smaller the stones. A single stone may completely fill the gall-bladder. If a few stones are present, they are usually polygonal and faceted, though the edges are rounded and the stones are usually smooth, though occasionally, a rough gall-stone is seen. As to *site,* they may occur in any part of the biliary tract. In over half the cases, they are confined to the gall-bladder; in many instances, there are stones in the cystic duct, or in the common duct, along with stones in the gall-bladder. Sometimes, there are stones in these ducts alone. Stones occur also in the hepatic ducts, but then there are nearly always stones elsewhere as well.

Chemical Composition.—The chemistry of gall-stones varies. They are classified (according to Naunyn) as (1) pure cholesterin, (2) laminated cholesterin with lime salts, (3) the mixed cholesterin stones (commonest), (4) the mixed bilirubin-calcium stones (about ¾ bilirubin-calcium and about ¼ cholesterin), (5) the pure bilirubin-calcium stones (always small stones), and (6) certain rare forms of stone.

In *consistency,* the cholesterin stones are the softest; the older stones are harder and more friable.

Formation.—The catarrhal cholecystitis is accompanied by epithelial desquamation, albuminous exudation, and increased formation of mucus and of cholesterin (derived from disintegration of the mucous cells lining the wall of the gall-bladder). The bilirubin-calcium is derived from the bile itself, through precipitation (by bacteria, or by the protein of the inflammatory exudate). Cholesterin stones are not formed within the intrahepatic duct; if found there, they have arrived by retrograde movement. Bilirubin-calcium stones may be formed in the intrahepatic ducts. Both varieties of stone may develop within the gall-bladder. For theories regarding the origin of gall-stones, see references.

Symptoms.—The principal symptoms of gall-stones are due to the **associated infection** of the biliary tract, which results (1) in *spasm* of the wall of the gall-bladder or of the bile ducts (with pain), (2) in *reflex disturbances* of the stomach and intestine (hyperchlorhydria, spasm, constipation, etc.), (3) in *adhesive pericholecystitis,* and (4) sometimes, in *perforation.*

The **mechanical effects** of the presence of gall-stones may also be very important, especially when the stone "wanders" through the biliary passages. There may be partial, or complete, obstruction of the ductus cysti-

cus, or of the ductus choledochus. The weight of gall-stones in an enlarged gall-bladder may cause discomfort.

French writers classify the mechanical phenomena as the "aseptic," the infectious phenomena as the "septic"; practically, it is often hard to distinguish between the two.

As W. J. Mayo has emphasized, gall-stones are rarely entirely *latent.* There are practically always accompanying symptoms of indigestion, described by Moynihan as "inaugural symptoms." These consist of fullness, weight and distention in the epigastrium soon after meals, relieved by belching (or instantly by vomiting), brought on especially by greasy foods. There is a feeling of tightness at the waist, relieved by bending forward, by flexing the right thigh, or by loosening the garments at the waist. Heartburn, sour regurgitation, and nausea are common symptoms. After an attack of indigestion there is soreness and stiffness in the right side for a few days. During the attack, chilly feelings, especially in the evening after a meal, and gooseflesh, are often noticed.

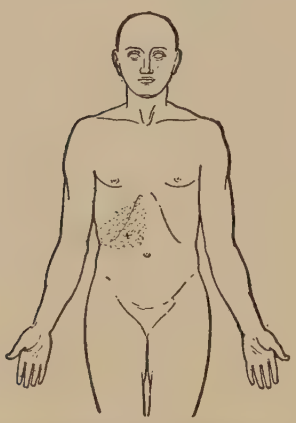

Fig. 425.—The Shaded Area Shows the Region of Cutaneous Hyperalgesia After an Attack of Gall-stone Colic. The + Is the Position of a Tender Point in Many Cases in Gall-stone Diseases and Is Over the Place Where a Twig of the Ninth Thoracic Nerve Passes Out of the Rectus Abdominis Muscle. (After J. Mackenzie, "Symptoms and Their Interpretation," published by Shaw & Son, London.)

The phenomena designated as **gall-stone colic** are usually characteristic. There is sudden severe pain in the right hypochondrium or in the epigastrium. It radiates to the back, or to the right shoulder, and is accompanied, usually, by nausea, vomiting, and symptoms of shock (tachycardia, feeble pulse, sweating). The pain may be followed, accompanied, or even preceded, by fever and chilly sensations. The duration of the attack varies from a few minutes to a few hours or longer. It may pass off suddenly, but is usually followed by aching and soreness for a few days. Calculi may sometimes be found in the sifted stools after an attack. On physical examination, signs of acute cholecystitis of greater or less degree can be made out in the right hypochondrium. It is probable that the dull pains are due to the cholecystitis, and that the more acute pains are due partly to an acute circumscribed pericholecystitis, partly to spasm of the smooth muscle in the gall-bladder or bile duct. Sometimes the pain is due to the actual passage of a gall-stone along the biliary tract, but less frequently than is commonly supposed. There is often tenderness on pressure in the lower part of the back of the chest on the right side.

It is a mistake to think that *jaundice* must occur in connection with gall-stones. A large proportion of the patients have gall-stones for years

without jaundice. Jaundice may, of course, occur (1) when there is impaction of a gall-stone in the common duct or in the hepatic duct, (2) from compression of the common duct or hepatic duct by a large stone in the cystic duct, or by inflammatory products, or (3) as a catarrhal jaundice (swelling of the mucosa). Even in the patients from whose common ducts stones have been removed, jaundice has previously been entirely absent in at least 25 per cent (Moynihan).

The *gall-bladder* may or may not be palpable. According to the well-known "Courvoisier's law," a contracted gall-bladder in chronic jaundice suggests gall-stones, while a dilated gall-bladder in chronic jaundice points to biliary obstruction due to causes other than gall-stones (especially to cancer of the head of the pancreas). According to the late Dr. A. O. J. Kelly, however, at least 40.5 per cent of 116 patients who had gall-stones and jaundice, also showed enlargement of the gall-bladder. In general, however, the "Courvoisier law" holds, since the inflammatory thickening and cicatrization of the gall-bladder resulting from the recurring infection in gall-stones leads to contraction.

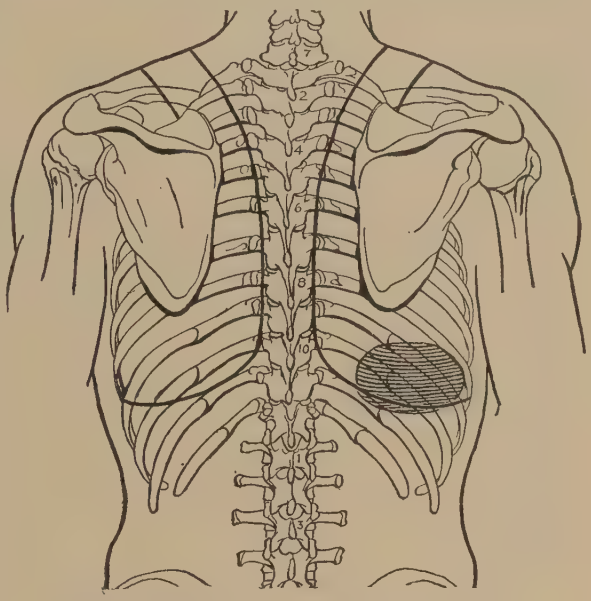

Fig. 426.—Dorsal Pressure-zone in Cholelithiasis.

On palpation, gall-stone crepitation can sometimes be felt, though rarely.

Stone in the ductus choledochus is very common, especially at its lower end. Usually, there is a single stone, which may cause either partial or complete obstruction. The ducts behind it become dilated, and the liver enlarged. In *complete obstruction,* there is persistent jaundice, with or without fever, depending upon whether there is outspoken infection or not. Long-continued obstruction of the common duct either by gall-stones or by tumors may lead to dilatation of all the biliary passages, the contents ultimately consisting not of bile but of a watery, clear fluid (*hydrops viarum biliferarum*). In *incomplete obstruction,* there may be no jaundice, but there is intermittent fever, usually with chills and sweats. There is always danger of complicating chronic pancreatitis in these cases.

In **obstruction of the ductus cysticus,** any one of several results may follow. The gall-bladder may become distended with mucus or with clear bile (*hydrops cystidis felleae*); sometimes an acute cholecystitis follows; more often, a shrunken, cicatricial gall-bladder results.

Of the *other complications* of gall-stones, purulent cholangitis, chronic pericholecystitis with adhesions, the formation of biliary fistulae (duodenal, colonic, pleural, external, etc.), and intestinal obstruction, are the more important.

Diagnosis.—This depends upon (1) the history of gall-stone colic; (2) the symptoms of recurring cholecystitis; (3) tenderness on deep palpation in the right hypochondrium; and (4) a thorough röntgenological examination, which, recently, has permitted of the demonstration of the existence of gall-stones in about half the cases, though negative x-ray find-

Fig. 427.—Röntgenogram Revealing the Presence of Gall-stones. (By courtesy of Dr. Baetjer and Dr. Waters, X-ray Dept., J. H. H.)

ings by no means rule out gall-stones (See Röntgenological Examination).

Gall-stone colic must be differentiated (1) from *renal colic* (pain beginning in the back and radiating along the ureter to the testicle or vagina, dysuria, hematuria, site of calculus in stereo-röntgenograms); (2) from *intestinal colic* (sequel to dietary indiscretion, central abdominal pain, ab-

sence of local tenderness in the right hypochondrium); (3) from *lead-colic* (anamnesis, blue line on gums, basophilic stippling of erythrocytes).

The "inaugural symptoms" of gall-stones (or attacks of indigestion de-

Fig. 428.—A Large Collection of Gall-stones Beautifully Revealed by an X-ray Photograph. (Courtesy of Dr. Jas. T. Case.)

pending thereupon) must be distinguished (4) from *gastric ulcer* (time of pain, x-rays); (5) from *duodenal ulcer* (hunger-pain, occult blood, x-ray, seasonal periodicity); in long-standing cases (6) from *carcinoma of the gall-bladder* (nodular enlargement, emaciation, cachexia).

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2. Neoplasms of the Biliary Tract

(*a*) *Cancer of the Gall-bladder*

(Carcinoma vesicae felleae)

Occurrence.—This is nearly always primary, and it occurs almost exclusively in gall-bladders containing stones. It is usually infiltrating.

Unfortunately, it is not an uncommon disease. Like gall-stones, it is more often seen in women than in men (3 or 4:1). It occurs most often between fifty and sixty. It has been estimated that from 4 to 14 per cent of patients suffering from gall-stones develop cancer of the gall-bladder (Rolleston).

Cancer sometimes develops in the ampulla of Vater behind the papilla duodeni, but cancer here does not seem to be related to gall-stones. Cancer of the bile ducts elsewhere also seems to be independent of gall-stones.

In the gall-bladder, the fundus is most often the site of a beginning cancer; sometimes the neck is first involved. In half the cases, there is extension to the adjacent liver.

Symptoms.—On account of the catarrhal cholecystitis and cholelithiasis, which nearly always precede the occurrence of cancer of the gall-bladder, it may be exceedingly difficult to recognize the beginning of the malignant disease. Should enlargement of the gall-bladder and jaundice appear, however, in an elderly patient with gall-stones, or the general health be impaired, the region of the gall-bladder may on careful palpation be felt as a *nodular mass* adherent to the liver, and tender. There is *jaundice* in about 75 per cent of the cases, most often due to extension of the cancer into the biliary ducts, or to pressure upon them from without. *Ascites* occurs in about 25 per cent of the cases, usually due to carcinosis of the peritoneum, or to peritonitis. Cancer of the gall-bladder terminates fatally in a few months.

Diagnosis.—If there be a history of gall-stones, and a hard nodular mass develop in the region of the gall-bladder, accompanied by jaundice, emaciation, and a beginning cachexia, the diagnosis is clear. Unfortunately, it is uncommon for the symptoms and signs to permit of a diagnosis early enough for successful surgical removal, though occasionally this may happen, and we should be on the lookout for the disease.

In the differential diagnosis, we must try to distinguish cancer of the gall-bladder (1) from *simple gall-stones;* (2) from *carcinoma hepatis;* (3) from *carcinoma pancreatis;* and (4) from *carcinoma of the ampulla of Vater or of the biliary ducts.*

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J. Special Diagnosis of Diseases of the Peritoneum

The diseases of the peritoneum, or the peritoneopathies, include:

I. The *peritoneopathies of circulatory origin* (ascites, and hemoperitoneum).

II. The *inflammatory peritoneopathies* (acute peritonitis, chronic peritonitis, specific forms of peritonitis).

III. The *parasitic peritoneopathies* (hydatid cysts of the peritoneum).

IV. The *neoplastic peritoneopathies* (primary sarcoma, endothelioma and lipoma, secondary carcinoma and sarcoma, non-parasitic cysts).

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1. The Peritoneopathies of Circulatory Origin

Under this heading we shall describe (1) ascites, and (2) hemoperitoneum, and shall refer briefly to choleperitoneum, though it is a disorder of the biliary circulation, not of the blood-vascular apparatus.

(*a*) *Ascites*

(*Seroperitoneum; Hydroperitoneum; Peritoneal Effusion*)

Definition.—The term ascites has been rather loosely used. It is now commonly employed to mean the presence of free fluid in the peritoneal cavity, just as pleural effusion means the presence of free fluid in the pleural cavity. This fluid may be either a *transudate* (hydroperitoneum, or non-inflammatory seroperitoneum), or it may be an inflammatory *exudate*.

Etiology.—An ascites depending upon *transudation* occurs (1) in chronic circulatory insufficiency due to any cause; (2) in obstruction to the inferior vena cava between the right side of the heart and the hepatic

veins; (3) in portal obstruction (cirrhosis hepatis, lues hepatis, carcinoma hepatis, or portal thrombosis). An ascites due to *inflammatory exudate* may occur in various forms of peritonitis (simple infectious, tuberculous, carcinomatous).

Characters of the Fluid.—The fluids present in ascites have been referred to in Section III (Exploratory Punctures). It has there been pointed out how to distinguish a transudate from an exudate, and the bacteriodiagnostic, cytodiagnostic and immunodiagnostic methods are also there discussed.

Chylous ascites, in which there is escape of chyle from the lymphatics, contains finely divided fat, but does not contain leukocytes, or other cells in large numbers, showing fatty change.

In *chyliform or fatty ascites* there is no leakage of chyle, though fat is formed in the peritoneal effusion; the fat globules are large, and cells containing fat are present in the fluid. It is usually dependent upon neoplasm, though it may occur with either simple or tuberculous chronic peritonitis. It is very much more common than true chylous ascites.

In *milky, non-fatty, or lactescent, ascites,* the opacity is not due to fat, but to some other substance, often a protein, or a lecithin. Layers are not formed on standing. The condition is sometimes met with in neoplasm.

Symptoms of Ascites.—On *inspection,* the enlargement of the abdomen may be slight at the beginning, but in old cases extreme measurements may be met with. Duncan has reported a woman who measured 11 feet around the abdomen; at autopsy there were 47½ gallons of fluid in the abdominal cavity.

Fig. 429.—Ascites from Cirrhosis of the Liver. (Med. Service, J. H. H.)

When the fluid first accumulates, the prominence is chiefly above the umbilicus and the antero-posterior diameter of the abdomen is increased. On longer duration, the muscles of the abdomen will become flaccid and atrophic, and one sees diastasis of the recti and bulging in the flanks. The intra-abdominal pressure is increased.

In portal obstruction,

the dilated veins can be seen through the tight, shiny skin. The central veins, especially, are enlarged, and, in extreme ascites, the lateral veins also (from compression of the inferior vena cava). After tapping, the lateral veins collapse, though the central veins continue to be dilated.

The umbilicus is often everted. The inferior aperture of the thorax is expanded, and respiration is largely thoracic. On *palpation,* a fluctuation-wave can be obtained if the flat of the hand be placed on one side of the abdomen and the opposite side be tapped, or flicked, with the finger. This sign comes out well if a third person depress the middle line of the abdomen with the ulnar surface of one hand. An enlarged liver or

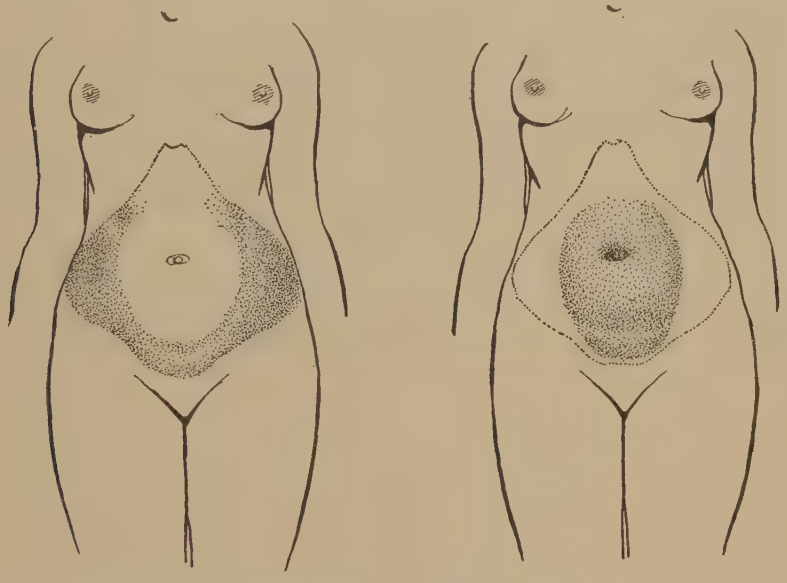

Fig. 430.—Comparative Results of Abdominal Percussion in Ascites and in Ovarian Cyst—the Dull Areas Are Shaded.

spleen, or an abdominal tumor, if present, can be palpated through the fluid by "dipping."

On *percussion,* a horseshoe-shaped area of dullness first appears, the tympanitic umbilical and epigastric regions in its concavity, and shifting dullness is demonstrable in the flanks, if the fluid be free and the intestines contain gas.

The patients complain of *pain* due to stretching of the abdominal walls, and they suffer also from *dyspnea, indigestion,* and *constipation.*

In extreme ascites, the pressure on the inferior vena cava may cause chronic passive congestion of the kidneys (oliguria, albuminuria, cylindruria) and edema of the lower half of the body. The apex beat is dislocated upwards owing to the displacement of the diaphragm.

Diagnosis.—Abdominal distention, a fluctuation-wave, and shifting dullness in the flanks, especially if there be also a demonstrable cause for the existence of the ascites, make the diagnosis clear.

In searching for causes, several points are of importance. In children and in young women, tuberculous peritonitis is common. In adults over forty, cirrhosis hepatis, chronic peritonitis, and cancer should be thought of.

The character of the fluid obtained on tapping will distinguish between a transudate and an exudate (see Section III), and the physical, chemical and biological characters of the fluid may throw light on its origin.

If jaundice coexist, a slight degree suggests cirrhosis hepatis, an intense jaundice, malignancy.

An ascites that recurs after repeated tappings may be due to cirrhosis hepatis, but is most often due to chronic hyperplastic peritonitis.

Fever, old scars in the neck, and concomitant pleurisy or tuberculosis, make a tuberculous peritonitis probable; the *ascite des jeunes filles* is a tuberculous peritonitis and is most common just before puberty. I saw a case with Dr. H. F. Hill, of Baltimore, in which there was great distention after rapid development. On operation, the peritoneum was studded with tubercles. The girl made a good recovery.

If desired, a fine cystoscope can be passed through a trocar after air has been introduced following paracentesis—so-called *laparoscopy*. By this method Jacobaeus asserts that he was able to recognize the cause of an ascites!

In the **differential diagnosis,** we must distinguish ascites (1) from *large ovarian or parovarian cysts* (mode of development, maximal growth low, upper or lateral displacement of umbilicus, median dullness); (2) from *hydatid cyst* (often multiple, "canine history," eosinophilia, complement-fixation); (3) from *large pancreatic cyst;* (4) from *hydronephrosis;* (5) from *encysted peritonitis;* (6) from *immense fatty tumor* (rare); (7) from *distention of the urinary bladder* (catheter!); (8) from *extreme dilatation of the stomach* (bismuth x-ray); (9) from *pregnancy with hydramnios;* (10) from *extreme obesity with tympanites;* and (11) from *chronic intestinal obstruction with dilatation of the intestine with fluid proximal to the obstruction.*

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[Discussion], 1298.

(*b*) *Hemoperitoneum*

Definition.—The presence of pure blood free in the peritoneal cavity, as distinguished from a blood-stained ascitic effusion.

Etiology.—The commonest cause is rupture of an extra-uterine pregnancy. Other causes include traumatic rupture of one of the abdominal organs, rupture of aneurism, hemorrhage from an angioma or angio-sarcoma, and rupture of varicose veins.

I have seen one fatal case of hemoperitoneum follow exploratory puncture of the spleen by a colleague; the puncture was done in the early nineties for malarial diagnosis. I made the autopsy, and found a large quantity of blood in the peritoneal cavity and a slit 1 cm. long in the capsule of the spleen; it was due to the fact that the patient suddenly took a deep breath at the moment the needle was inserted.

Symptoms.—The patient presents the symptoms of internal hemorrhage (faintness, tachycardia, restlessness, dyspnea, pallor). There may also be vomiting, colicky pains in the abdomen, sweating, and collapse.

Should the patient survive, fever develops, and unless operation is undertaken, peritonitis sets in, since a hemoperitoneum soon becomes infected.

Diagnosis.—After trauma, the condition will often be suspected, but in ruptured extra-uterine pregnancy the condition is often overlooked or may be confounded with acute perforative peritonitis until laparotomy is done. If hemoperitoneum be recognized promptly, a life may often be saved by immediate surgical treatment.

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(*c*) *Choleperitoneum*

(Biliary Peritonitis)

Definition.—The presence of bile in the peritoneal cavity as a result of rupture of the bile passages.

Symptoms.—Ordinarily, a rupture of the biliary tract into the peritoneal cavity causes an acute peritonitis, owing to the fact that the bile is usually infected. In case the bile is aseptic, inflammation need not result. Large aseptic bilious effusions have been designated "choleperitoneum" (Dévé). The condition most often follows rupture of a hydatid cyst communicating with the bile duct. Choleperitoneum has also been observed in association with cholecystitis without perforation (Johannson, Wolff).

There is, as a rule, slight enlargement of the abdomen, without fever or jaundice. On tapping, the character of the fluid is seen. Recurrence is common.

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2. The Inflammatory Peritoneopathies (Peritonitis)

Inflammation of the peritoneum may be acute or chronic, circumscribed or diffuse. It may be due to simple bacterial infection, or to infection with tubercle bacilli.

(*a*) *Acute Peritonitis*

This may be either (1) general or diffuse, or (2) circumscribed or localized.

i. Acute General Peritonitis

(Acute Diffuse Peritonitis; Acute Universal Peritonitis; Acute Progressive Peritonitis; Acute Non-circumscribed Peritonitis)

Definition.—By acute general peritonitis is meant an inflammation of the peritoneum that sets in suddenly, and is not strictly localized, but tends to spread throughout the whole of the abdomen.

Etiology.—The peritoneum most often becomes secondarily infected as a result of an infected local lesion in the abdomen. This may be *exogenous,* as in the case of a perforating wound, or *endogenous,* when the infection originates in an abdominal viscus (*e. g.,* perforation of the stomach, small intestine, appendix, colon, or gall-bladder; or rupture of

an abscess of the liver, spleen or lymph gland; or leakage from a pyosalpinx; or a perforated uterus).

Less commonly, acute diffuse peritonitis is of *hematogenous* origin (Flexner's "primary" peritonitis). This form is common (1) as a "terminal infection" in run-down conditions (carcinoma, chronic nephropathies, or advanced arteriosclerosis); (2) in general sepsis; and (3) as a metastatic infection from the tonsils or other primary focus of infection. In the epidemic of septic sore throat that has recently prevailed in American cities, metastatic peritonitis has not been uncommon, especially in young women. The term "primary idiopathic peritonitis" is best avoided, though by it a hematogenous peritonitis is usually meant.

In young children, acute peritonitis is most often secondary to perforation of the appendix. Soon after birth, however, acute peritonitis may result from infection at the umbilicus.

In *perforative peritonitis,* there is nearly always a mixed infection, though the *Streptococcus pyogenes,* the *Bacillus coli* and the *Staphylococcus epidermidis albus* (Welch) are the most common causes. Other bacteria not infrequently met with are the *Staphylococcus pyogenes aureus,* the *Bacillus pyocyaneus,* the *Bacillus typhosus,* and the *Bacillus influenzae.* The *Pneumococcus* is not infrequently a cause of peritonitis, either by metastatic infection, or in perforative peritonitis.

In pelvic peritonitis, except that of the puerperium, *gonococci* are often responsible. In puerperal peritonitis, *streptococci* are usually the cause.

Symptoms.—These depend upon (1) the cause of the peritonitis, and (2) the virulence of the bacteria.

Perforative peritonitis is the most common form. The patient is suddenly seized with extreme pain in the abdomen, followed by collapse. At first, the abdominal wall is contracted rigidly and is very tender. The pain is diffuse and extremely severe; abdominal respiration ceases, and severe vomiting sets in. After a few hours, the patient feels better (stage of "repose" or latency). The appearance, however, is fallacious. Soon the signs of peritonitis become unmistakable; tympanites appears, and the patient unconsciously tries to relax the abdominal wall by drawing up his legs and by lying with his arms above his head. The pain continues with exacerbations, and the least movement exaggerates it. There is recurrent vomiting, thirst, fever, leukocytosis, a small, wiry pulse, and a Hippocratic facies (pale, sunken, pinched, anxious). The picture is that of grave toxemia with progressive exhaustion. The superficial liver dullness disappears soon after the perforation. Toward the end, the pulse grows more rapid and feebler; there is an increase of the abdominal distention; the skin is cold and clammy, and the extremities blue;

the mind may remain clear to the end. Shortly before death, the vomiting, pain, and tenderness may cease.

The clinical symptoms are due to (1) the widespread inflammation of the peritoneum, (2) the paresis of the wall of the bowel, (3) the absorption of toxins from the abdomen and from the lumen of the intestine, (4) the absorption of water from the tissues, and (5) sometimes, though not often, a bacteriemia.

Death may occur, in the severer forms, within forty-eight hours from the onset; ordinarily, it is postponed for four or five days. Fortunately, if operation be done within the first eight or ten hours after onset, many patients can be saved. The outlook is better in perforation of a gastric or duodenal ulcer than in perforations lower down, owing to the relatively small number of bacteria in the upper part of the gut.

In **puerperal peritonitis,** due most often to streptococcus infection, the toxic symptoms are marked. There is usually diarrhea and outspoken tympanites. Vomiting may not be prominent. It is often accompanied by septicemia, thrombophlebitis, or metastatic infection of serous membranes (pleura, pericardium, joint cavities).

In **pneumococcic peritonitis,** the peritoneum may become infected metastatically through the blood stream from a pneumonia, an otitis media, or a sore throat. Less commonly, it extends from an appendix infection or other abdominal focus, from the pleura through the diaphragm, or through the fallopian tubes.

Pneumococcic peritonitis is commoner in children than in adults, occurring not infrequently in very young infants. Up to puberty, girls are two or three times as often affected as boys. The peritonitis may become localized; in half the cases a residual abscess forms, usually pointing near the umbilicus. The condition is often mistaken for appendicitis, typhoid fever, or tuberculous peritonitis.

In **gonococcic peritonitis,** the cocci reach the peritoneal cavity from the fallopian tubes in the female; it rarely occurs in males, but may do so by extension through the lymphatics of the spermatic cord. The resistance of the peritoneum appears to be markedly diminished just before the menstrual period. The inflammation sets in suddenly with severe symptoms. Young girls are often affected, and gonococcic peritonitis is more fatal in children than in adults. Since the lower abdomen is first involved, the condition is sometimes taken to be appendicitis.

Diagnosis of Acute Peritonitis.—The sudden onset, the anamnesis, and the occurrence of violent pain with abdominal distention, vomiting, immobility of the abdomen, constipation, and symptoms of collapse, are, as a rule, unmistakable. (For the diagnosis of typhoid perforation preceding the development of peritonitis, see Typhoid Fever.)

Where an acute general peritonitis is threatened, the physician must give himself over to watching the patient, at least for a few hours, or

until the diagnosis is clear. The character of the pulse, the behavior of the leukocytes and of the blood pressure, the palpatory findings in the abdomen, and the disappearance of superficial hepatic dullness, should be kept in mind. The use of morphin or opiates to relieve the pain should be avoided, at least until the diagnosis is sufficiently clear.

So-called *latent* forms of acute peritonitis occur with almost no symptoms, but these are usually in greatly exhausted patients near death from cancer, chronic nephropathy, or other hopeless diseases (terminal infections); in such cases, operation would, anyhow, be of no avail. In the acute peritonitis that follows laparotomy, there may be no symptoms except vomiting and tachycardia (Rolleston).

In the **differential diagnosis** we must distinguish acute general peritonitis (1) from *severe colics* (hepatic colic, renal colic, lead colic); (2) from *acute intestinal obstruction before its accompanying peritonitis sets in* (afebrile, absence of abdominal rigidity, more profuse vomiting, pain colicky and not continuous); (3) from *acute hemorrhagic pancreatitis;* (4) from *hemoperitoneum* (signs of internal hemorrhage); (5) from *peritonism* (due to torsion of the pedicle of an ovarian cyst, of a floating kidney, of a wandering spleen, or of an undescended testicle, or to mesenteric hemorrhage, or to hysteria); (6) from *enteralgia* (history of similar attacks); (7) from *acute enteritis* (severe diarrhea, colicky pains).

When possible, the *cause* of an acute peritonitis should be determined before operation, since this may govern the surgeon in his choice of the site of incision. Rolleston gives the following diagnostic hints for etiological diagnosis:

1. In *children,* sudden peritonitis is most often due to fulminating appendicitis though pneumococcic and gonococcic peritonitis may occur.

2. In *young women,* the commonest causes are (a) perforated gastric ulcer, and (b) pelvic infection.

3. In the *anamnesis,* gastric disturbances in young women suggest perforated gastric ulcer; in people over 50, perforation from carcinoma ventriculi. A peritonitis following gastro-enterostomy for gastric ulcer makes one think of a perforation of a jejunal ulcer; a peritonitis in the course of typhoid fever, of perforation of an ulcer of the ileum; a peritonitis in the course of pelvic abscess, of pelvic peritonitis. The site of the first violent pain may be helpful, especially in perforative appendicitis, but it is not pathognomonic for localization.

A sudden peritonitis in persons apparently perfectly healthy before may be due, in children, to fulminating appendicitis; in young women, to perforation of a latent gastric ulcer, and in men, to perforation of a latent duodenal ulcer.

ii. Acute Circumscribed Peritonitis

This may be (1) simple adhesive, or non-purulent, or (2) purulent.

1. *Non-purulent Acute Circumscribed Peritonitis*
(*Acute Non-suppurative Circumscribed Peritonitis*)

Occurrence.—The condition is very common as a result of extension of inflammation from an underlying organ to its peritoneal covering. It accounts for the adhesions around ulcers of the stomach, duodenum and colon, around a chronic appendicitis, around an inflamed gall-bladder, etc. In a sense, it is a protective measure, often shutting off a threatened perforation of an ulcer, or of an abscess, from the general peritoneal cavity. The *adhesions* that are formed may, however, menace the general health subsequently, often being the cause of abdominal pain, or of disturbances of digestion; and, sometimes, the adhesions or bands formed may be the cause of a chronic intestinal obstruction, or of an acute obstruction from internal hernia or from strangulation.

Among the *special forms* of acute non-suppurative circumscribed peritonitis, we may mention (1) acute perigastritis, (2) acute periduodenitis, (3) acute periappendicitis, (4) acute pericolitis (including acute perisigmoiditis), (5) acute pericholecystitis, and (6) acute epiploitis (inflammation of the great omentum).

2. *Purulent Acute Circumscribed Peritonitis*

Under this heading, we include the various local abscesses that develop in the peritoneal cavity as a result of purulent peritonitis. The three commonest forms are (1) *appendix abscess,* (2) *subphrenic abscess* (due to appendicitis, hepatic abscess, splenic abscess, perforated gastric or duodenal ulcer, or other cause), (3) *purulent peridiverticulitis* (in the left iliac fossa); the less common forms are (4) *perigastric abscess,* (5) *pericolic abscess,* and (6) *residual peritoneal abscess.* Other abscesses may occur in close connection with the peritoneum, namely, (7) *mesenteric abscess,* (8) *omental abscess,* and (9) *retroperitoneal abscess.*

Many of these conditions are described in connection with their primary cause (see Appendicitis, Peridiverticulitis, Duodenal Ulcer, etc.). Here we shall describe, especially, subphrenic abscess.

Subphrenic Abscess

Definition.—By a subphrenic abscess is meant a collection of pus in contact with the under surface of the diaphragm (exclusive of abscess in the liver and abscess in the spleen).

Varieties.—Two forms occur: (1) the non-gaseous or simple subphrenic abscess, and (2) the gas-containing subphrenic abscess, or subphrenic pyopneumothorax. The two forms occur with equal frequency.

Non-gaseous or Simple Subphrenic Abscess

This is due to infection with pyogenic bacteria, usually by extension from, or perforation of, some organ in the neighborhood, though the abscess may be secondary to a distant process like an appendicitis, or a pyosalpinx.

The most common cause is appendicitis, especially that occurring in a retrocecal appendix, but leakage from an hepatic abscess or minute perforations of the stomach, duodenum or colon may be responsible. Other causes include, extension from purulent pancreatitis, from perinephritic abscess, from pelvic abscess, or from an abscess of the spine.

Subphrenic abscess may be either intraperitoneal or extraperitoneal, more often the former. Most of the abscesses are on the right side.

Barnard has made a most careful study of the anatomical boundaries of subphrenic abscesses, describing six forms, corresponding to six areas on the under surface of the diaphragm, four of them intraperitoneal, two extraperitoneal. His paper should be studied in connection with any case under observation.

In half the cases, the inflammation extends to the adjacent pleural cavity. The extension may occur through the lymphatics, or the diaphragm may be perforated, in which event empyema, abscess of the lung, or gangrene, may develop.

Symptoms.—The onset is, as a rule, gradual, and preceded by the symptoms of the primary disease causing it. The symptoms may be vague at first (fever, tachycardia, suggestive signs at the right base).

The physical signs may be mainly thoracic (dullness at one base behind, bronchial breathing, friction rub); or mainly abdominal (pain, tenderness and prominence in one hypochondrium, or in the epigastrium, restriction of respiratory movements, rigidity, palpable tumor, dullness on percussion, sometimes edema, redness and fluctuation). In nearly all cases, there is fever, tachycardia, and outspoken polymorphonuclear neutrophilic leukocytosis; sometimes there are chills and sweats.

Diagnosis.—The physician will do well to remember the possibility of the occurrence of subphrenic abscess after various acute abdominal conditions. In the absence of a recognizable antecedent, a palpable swelling may be the first clew.

After laparotomy for removal of an appendix, or for gall-stones, if signs of purulent infection persist, or if they appear, not having been present before, a physical examination of both backs should be carefully made and a thorough röntgenoscopic and röntgenographic study undertaken. If local signs be discovered, systematic exploration with a Record syringe and a long needle should be made under anesthesia. Barnard recommends exploring first the 10th intercostal space in the scapular line. If no pus be found, the 9th, 8th, 7th and 6th spaces are successively punctured. Should all these punctures be negative, the same spaces in the midaxillary line are next explored from below upward. Subphrenic abscesses presenting in front should not be punctured. If pus be found, the operation for evacuating it should be at once proceeded with, while the patient is still under the anesthetic.

In the **differential diagnosis,** we must distinguish subphrenic abscess (1) from *abscess of the liver* (liver enlarged downward, x-rays); (2) from *retroperitoneal sarcoma on the left side;* (3) from *purulent or non-purulent pleural effusion,* especially when pleural effusion complicates subphrenic abscess (different fluids obtained by exploratory puncture at two levels; *Fuerbringer's sign,* a needle in a cavity above the diaphragm is immobile on respiration, but if it pass through the diaphragm, the extrathoracic part of the needle moves upward on inspiration and downward on expiration; *Pfuhl's sign,* a needle in a subphrenic abscess, reveals a higher pressure and a greater flow of pus during inspiration than during expiration, the reverse being true in empyema).

Gas-containing Subphrenic Abscess, or Subphrenic Pyopneumothorax

Etiology.—It is most often due to (1) perforation of a gastric ulcer, though it is less common since such perforations have come to be treated immediately by operation. Other causes include, (2) perforated duodenal ulcer, (3) rupture of an abscess or of a suppurating hydatid cyst into the gastro-intestinal tract, and (3) development of gas in a subphrenic abscess secondary to appendicular abscess.

Women between twenty-five and forty years of age are most often affected.

Situation.—While non-gaseous subphrenic abscesses are commoner on the right side, gas-containing subphrenic abscesses are nearly all on the *left* side, owing to their origin from perforated gastric ulcers.

Symptoms.—The onset is sudden and violent, owing usually to perforation of a gastric ulcer. The pain is in the epigastrium or the left hypochondrium. There is severe vomiting, tenderness, and abdominal distention, with fever, tachycardia, and leukocytosis.

On physical examination, the signs suggest pneumothorax or pyopneumothorax (*q. v.*), but the heart is displaced upward and not much to the right. In the rare right-sided cases, the liver may be shoved markedly downward. Extension to the pleural cavity is common.

Diagnosis.—As Rolleston emphasizes, the history and mode of onset point to the abdomen, while the physical signs suggest a pyopneumothorax. The failure of the heart to be displaced to the right, and, above all, x-ray examination, easily differentiate.

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(*b*) *Chronic Peritonitis*

Chronic peritonitis may be (1) simple, non-tuberculous or (2) tuberculous. The former may, in turn, be (i) circumscribed or (ii) general.

i. Circumscribed Simple Chronic Peritonitis

(*Localized Chronic Peritonitis*)

Occurrence.—Two forms are met with: (1) *chronic adhesive peritonitis* as a sequel to a preceding acute peritonitis and giving rise to adhesions of the parietal peritoneum to the visceral peritoneum, or to colonic membranes and bands, sometimes causing kinkings or local obstructions to the intestine (Lane's kink, etc.); and (2) *localized chronic progressive peritonitis,* in which, as a result of the continuance of the irritation, the chronic inflammation persists, and extends for a long time. The latter form includes: chronic pelvic peritonitis, so common in women, chronic periappendicitis, chronic pericholecystitis and chronic membranous pericolitis (Jackson), though the latter may, sometimes, be a part of the developmental adhesive peritonitis that occurs before birth. In the left iliac fossa, chronic peridiverticulitis and perisigmoiditis may give rise to much thickening and to intestinal obstruction. It has already been described under diseases of the intestine.

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ii. General Simple Chronic Peritonitis

(Diffuse Chronic Peritonitis, Chronic Progressive Peritonitis, Chronic Proliferative Peritonitis, Chronic Indurative Peritonitis, Multiple Progressive Hyaloserositis, Concato's Disease, Peritonitis deformans, Peritonitis fibrosa, etc.)

Definition.—A group of conditions in which there is a general chronic progressive inflammation of the peritoneum, differing from ordinary tuberculous peritonitis, and standing in no relation to malignant disease.

Etiology.—This form of chronic peritonitis may be a part of a polyserositis (Concato's disease), and is especially often associated with chronic indurative mediastinopericarditis, of which Pick's pericardial pseudocirrhosis (*q. v.*) is a part.

A similar chronic peritonitis occurs in association with arteriolar nephropathy. Other cases occur, associated neither with polyserositis nor with arteriosclerosis.

There is a growing feeling that this peculiar form of peritonitis may in reality be an especial form of tuberculous disease, presenting entirely different characters from ordinary tuberculous peritonitis. Many feel that the condition may be due to any one of several microörganisms (*Bacillus tuberculosis, Bacillus typhosus, Bacillus coli*). The etiology is not yet wholly clear.

The *sexes* are equally affected. The disease is most often met with in *middle life,* but may occur at any age.

The changes in the peritoneum may vary from very slight opacity to the formation of thick membranes 6 mm. or more thick. The thicker membranes are found especially around the liver and spleen (so-called "icing" liver, or *Zuckergussleber* of Curschmann (see Perihepatitis). In many cases the omentum is shortened and rolled up as a transverse mass across the abdomen; the mesentery is retracted, anchoring the intestine close to the spine; the total length of the

intestine may be greatly shortened, with accentuation of the valvula conniventes, which are crowded close together, looking, on longitudinal section of the bowel, like a comb. I remember a specimen in Prof. Welch's laboratory that strikingly illustrated this condition, and Rolleston refers to the same case in his article on Diseases of the Peritoneum in Osler's System. When the disease advances to this degree, it is well designated "peritonitis deformans."

Symptoms.—Clinically, the picture is that of a *chronic recurring ascites* without apparent cause, often requiring tappings every week or so for years. The *physical signs* are those of ascites (*q. v.*). After paracentesis, palpation may reveal a transverse mass, due to rolled up omentum. Sometimes there is absence of the tympany ordinarily met with in the middle of the abdomen in ascites, owing to retraction of the mesentery, with anchoring of the small bowel to the spine. The coincidence of the signs of ascites with chronic obliterative pericarditis or pleuritis, or with arteriolar nephropathy, help in making the diagnosis.

Differential Diagnosis.—We must distinguish chronic deforming peritonitis (1) from ordinary *tuberculous peritonitis;* (2) from *carcinoma* of the peritoneum; and (3) from ascites due to *cirrhosis hepatis.*

For references, see under Capsular Cirrhosis of the Liver.

(*c*) *Tuberculous Peritonitis*

Definition.—Tuberculous infection of the peritoneum, usually, though not always, associated with fluid peritoneal effusion.

Occurrence.—The disease is much more common than is ordinarily suspected. Many of the cases remain undiagnosed. Tuberculous peritonitis is often unexpectedly met with at abdominal operations or at autopsy. Since physicians are becoming more familiar with the disease, however, fewer cases go unrecognized than formerly.

Etiology.—The disease is most common in the third and fourth decades of life, though it may occur at any age. It is rather uncommon in infancy, and it has nothing to do with chronic enterocolitis (tabes mesenterica), with which it was formerly confused.

The infection is due to the *Bacillus tuberculosis,* and it is an interesting fact that, in over half the cases especially investigated, it has been due to the bacillus of the *bovine* type. This is probably due to the fact that the peritoneum is most often infected by a lymphogenous path from tuberculosis of the intestine, vermiform process, or lymph glands. In young women, the bacillus often reaches the peritoneum from the fallopian tubes. Hematogenous infection sometimes occurs. There is a remarkable discrepancy between German statistics and English statistics regarding the relationship of tuberculous peritonitis to primary intestinal tuberculosis.

British statistics indicate a frequent relationship; German statistics point to extreme rarity.

Symptoms.—Aside from *miliary tuberculosis* of the peritoneum, which is a part of a generalized miliary tuberculosis, tuberculosis of the peritoneum is divisible into three main types: (1) the *ascitic type;* (2) the *loculated type,* which may be either purulent or serous; and (3) the *obliterative* or *chronic fibroid* type.

In the **ascitic type,** the effusion develops gradually; the abdominal symptoms are often mild, though there is some discomfort; the general health and strength of the patient deteriorate. The abdomen is tender on pressure. If the effusion be large, it may compress the inferior vena cava and cause slight edema of the lower extremities. The punctate is characteristic of a tuberculous effusion (See Part III).

In the **loculated form,** the effusion is encysted and may lead to confusion with an abdominal cyst or with a solid or semisolid tumor. The general symptoms resemble those of the ascitic form, but the effusion is not free in the abdomen. The loculated effusion varies in its location. On palpation, masses due to adherent coils of the intestine, or to rolled up omentum, or to enlarged glands, may be felt. The condition may simulate an appendix abscess, a localized pneumococcic abscess near the umbilicus, or a pelvic abscess.

In the **obliterative or chronic fibroid form,** sometimes spoken of as the "dry" form, in contrast with the two preceding forms, which are "wet," the symptoms are those of chronic indigestion, sometimes of chronic intestinal obstruction. The patients emaciate and the general condition deteriorates. The skin and hair are harsh and dry, the skin being often pigmented. The thickened omentum is often palpable.

Among the *complications,* or the *concomitants* that occur in tuberculous peritonitis, may be mentioned, (1) intestinal tuberculosis, (2) pleural or pulmonary tuberculosis, (3) meningeal tuberculosis, and (4) general miliary tuberculosis.

Acute symptoms developing in the abdomen may be due to a fresh eruption of miliary tubercles, to rupture of a tuberculous gland, or to perforation of a tuberculous ulcer. These acute symptoms may be mistaken for an acute appendicitis, an acute cholecystitis, or an acute pelvic peritonitis. Acute or chronic obstruction of the intestine is not so very uncommon as a complication.

Diagnosis.—In young people, especially in women, the occurrence of ascites should always make one think of the possibility of a tuberculosis of the peritoneum. The *ascite des jeunes filles,* as has already been said, is nearly always a tuberculous peritonitis.

The *fever* may be slight in the ascitic form and in the obliterative form, though it is often quite high in the acuter cases, and especially in the purulent encysted type. The *urine* contains less indican than that of

acute peritonitis. Ehrlich's diazo-reaction is present in less than half the cases (L. Hamman). The urine is scanty and frequently contains albumin and a few casts.

The *blood* shows no characteristic changes, though usually there is a slight secondary anemia, and in about 1/3 of the cases a moderate leukocytosis, due probably to complications rather than to the tuberculous peritonitis itself.

In the **differential diagnosis**, the *acute* cases must be distinguished (1) from *typhoid fever* (no ascites, positive blood-culture, Widal test). The *chronic* cases must be distinguished (2) from *simple chronic peritonitis* (no fever, less pain, characters of punctate); (3) from *carcinoma* of the peritoneum (absence of other tuberculous foci, primary tumor, punctate); (4) from the ascites of *cirrhosis hepatis* (age, absence of tuberculosis elsewhere, alcoholism, punctate). It must be remembered, however, that tuberculous peritonitis is not an uncommon terminal event in cirrhosis hepatis.

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3. The Parasitic Peritoneopathies

Parasitic invasion of the peritoneum is not very common. Hydatid cysts represent the most important form. Cysticercus of the peritoneum is so rare as to be almost negligible. Nodules studded over the peritoneum resembling cysticercus

may be due to encystment of foreign bodies (seeds, etc.), entering the peritoneal cavity through rupture of an ulcer, when the resulting peritonitis is not fatal. Futcher and Follis have observed a remarkable instance of this condition.

(*a*) *Echinococcus Cysts of the Peritoneum*

(Hydatid Disease of the Peritoneum, Peritoneal Hydatidosis)

Occurrence.—In hydatid disease of the peritoneum, the peritoneum practically always becomes infected from rupture of, or leakage from, a single primary cyst of the liver. About two years after implantation, the cysts have grown large enough to cause symptoms or signs. Retroperitoneal hydatids, especially the so-called retrovesical hydatid cysts, may come from the peritoneum, or may have their origin in the bowel or in the blood vessels.

When due to the rupture of a preëxisting cyst, there may be a very large number of secondary peritoneal cysts, most abundant in the omentum and in the pelvic peritoneum. In *size*, the cysts vary from that of a pin-head to that of large palpable cysts. Through secondary infection with pyogenic cocci, the cysts may suppurate and cause local abscess, general peritonitis, or hepatic abscess.

Symptoms.—The abdomen gradually enlarges over a period of years. The symptoms may be those of ascites, or separate cysts may be either visible or palpable. The cysts are usually firm and movable. A thrill is rarely felt, and is not pathognomonic when felt. Pressure symptoms (indigestion, dyspnea, edema, pelvic symptoms) are common.

Diagnosis.—When the cysts are multiple and palpable, the condition should be suspected, particularly if a "canine history" is discovered. If the condition be suspected, eosinophilia and a positive complement-fixation test will be corroborative. Single cysts will almost always be taken to be something else (ovarian cyst, myoma uteri).

Cancer of the peritoneum runs so rapid a course that it is not likely to be mistaken for hydatids. Exploratory puncture should never be done if hydatids be suspected. Sometimes, however, a punctate unexpectedly reveals the presence of hooklets or scolices!

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4. The Neoplastic Peritoneopathies

Tumors of the peritoneum may be *malignant* or *non-malignant*. The most common malignant tumor is secondary cancer. Retroperitoneal sarcoma is also

clinically important. Primary malignant growths of the peritoneum are nearly always endotheliomata or sarcomata.

The *non-malignant tumors* may be solid or cystic. Of the *solid tumors,* fibromata, neurofibromata and lipomata are the most common. A *lipoma* may be very large, so large as to be mistaken for ascites, since these tumors are very soft. Of the *non-parasitic cystic tumors* of the peritoneum, mesenteric cysts, omental cysts, and peritoneal sanguineous cysts are the more common. Dermoid cysts, urachal cysts, and retroperitoneal cysts also occur. Some of these may be mistaken for congenital cystic kidney, for hydronephrosis, for pancreatic cysts, or for ovarian cysts.

On account of their importance, we shall describe a little more fully, (1) *retroperitoneal sarcoma,* and (2) *carcinosis peritonei.*

(*a*) *Retroperitoneal Sarcoma*

Occurrence.—This is met with most often in the right side of the abdomen—in the lumbar region, or in the middle line. Occasionally, it occurs in the iliac region, or in the pelvis. The cases were collected and analyzed by the late Dutton Steele. Over half the patients were between thirty and sixty years of age.

Symptoms.—An abdominal *tumor* is palpable, deep in the abdomen. It is usually fixed, and may be either smooth or nodular. Ordinarily, it is not tender. The patient may, or may not, notice the growth in the abdomen. It often causes *pain,* and sometimes digestive disturbances (vomiting, constipation). The *pressure symptoms* are variable (root pains, edema, ascites, collateral circulations). The *general condition* does not deteriorate as rapidly as in cancerous growths of the same size.

Diagnosis.—Though the mass can be felt, it may be impossible to be sure of its nature without surgical exploration and histological examination of an excised portion of the tumor. In differential diagnosis, it may be difficult to distinguish retroperitoneal sarcoma (1) from *inflammatory* growths or *"vanishing tumors"* (due to localized peritonitis following intestinal perforation, pancreatitis, actinomycosis); (2) from *tumors of the kidney or adrenal;* (3) from *pancreatic cysts;* (4) from *retroperitoneal teratoma and other benign tumors;* (5) from *carcinoma peritonei;* (6) from *tuberculous peritonitis;* (7) from *horseshoe kidney.* Even on surgical exploration, the diagnosis is not always clear.

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(*b*) *Carcinoma Peritonei*

(Malignant Peritonitis; Carcinosis Peritonei; Secondary Cancer of the Peritoneum)

Occurrence.—The disease is rather common, and is met with oftener in women than in men, on account of the frequency of cancer of the

uterus, of the breast, and of the gall-bladder, in women. It is rare before middle life. In either sex it may follow cancer of the stomach, rectum, intestine, pancreas, or other abdominal organ. When secondary to breast cancer, the invasion is through the lymphatics of the deep fascia of the abdominal wall (Handley's "Epigastric Invasion of the Peritoneum"). Secondary sarcoma of the peritoneum also occurs, but is less frequently met with than carcinoma.

Symptoms.—One observes, (1) *deterioration of the general health* (emaciation, cachexia), (2) the development of *ascites,* in which the punctate is often blood stained, chylous, or pseudochylous, and, (3) sometimes, palpable, *nodular masses* in the abdomen. Occasionally, small *metastases* can be seen or felt in the skin, especially at the umbilicus. *Pressure symptoms* may develop. Death occurs within six months after the peritoneum is invaded.

Diagnosis.—If a primary carcinoma is known to exist, the nature of developing peritoneal symptoms will usually be suspected. A hemorrhagic punctate in ascites should always excite the suspicion of either malignant disease or tuberculosis. Enlargement of the Virchow-Troisier gland above the left clavicle, or enlarged inguinal glands, are sometimes present, even when no tumor masses are palpable in the abdomen.

In the differential diagnosis, carcinoma of the peritoneum has to be distinguished (1) from *tuberculous peritonitis* (common); (2) from *hydatid cysts of the peritoneum* (rare); and (3) from *other causes of ascites* (cirrhosis hepatis, simple chronic peritonitis, thrombosis of the portal vein, etc.).

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Part IX

Examination of the Urine

A. Introduction

1. Significance of Examinations of the Urine

The examination of the urine yields information of two types: information as to normal and pathological metabolism; and information as to diseases of the kidneys and urinary passages.

The examination of urine for the data it yields as to metabolic processes is of great value to the clinician. The total output of urine gives him information as to the water equilibrium in the body and the simple determination of water retention, or of water elimination in excess of water intake, is often an indispensable aid (*e. g.,* in estimating the grade of myocardial insufficiency). The specific gravity is a gross measure of the solids excreted, a point (*e. g.,* in diabetes) of clinical interest. The reaction of the urine is of importance to the clinician through its relationship to the various conditions of acidosis in the body.

Under normal conditions the urine contains almost the entire amount of the end-products of protein metabolism; and a large proportion of the excess of mineral constituents is also excreted by this path. The feces and the sweat also contain small amounts of both. The fats and carbohydrates on the other hand leave the body mainly as CO_2 and H_2O through the lungs. In pathological deviations of the protein metabolism characteristic changes of a qualitative or quantitative nature occur in the bodies excreted in the urine (*e. g.,* the rise in the ammonia excretion in starvation; abnormalities in the uric acid excretion in gout). Moreover in certain diseases the metabolism of fats and carbohydrates is incomplete and allows of the accumulation of intermediary bodies, which then are eliminated in the urine (*e. g.,* the ketone bodies in acidosis; glucose in diabetes). The excretion of inorganic matter also shows abnormalities characteristic of certain diseases (*e. g.,* chlorid-retention in pneumonia). Thus the urine

enables us to detect certain perversions in the metabolism of all classes of foodstuffs, as well as to measure the normal metabolism of protein and of mineral constituents.

Certain foreign and toxic substances in the blood, arising from metabolic products or absorbed from the intestines are rendered innocuous and eliminated by the kidneys. Drugs and various poisons may be detected in the urine.

Equally important is the other type of information yielded by the urine—information as to disease of the kidneys or urinary passages. The various nephropathies, pyelitis, cystitis, etc., are detected largely by means of their characteristic urinary pictures. This aspect of the examination of the urine is too often in clinical practice allowed to lead to neglect of other equally important data.

A certain minimal routine examination of the urine of every patient should be regarded as essential. This routine examination should include:

1. The quantity passed in twenty-four hours.
2. The specific gravity.
3. The color.
4. The reaction.
5. Test for albumin (if positive, quantitative determination).
6. Test for sugar (if positive, determination of variety and quantitative determination).
7. Test for acetone or diacetic acid.
8. When the color is suggestive, special tests for bilirubin, hemoglobin, urobilin or other pigments.
9. Microscopic examination of the sediment.

It cannot be too strongly insisted upon that the examination of only single specimens of the urine can under no condition replace the routine examination of the total urine. The morphological elements in the urine are best studied in fresh specimens; certain qualitative tests when positive are decisive; in special instances it may be desirable to study the urine at different hours; in these ways the examination of a single specimen may be of great use. But negative tests in a single specimen must not be taken as decisive, and no conclusions as to the average specific gravity, reaction, color, or quantitative excretion of any normal or pathological urinary constituent can be drawn from single specimens. With lack of knowledge of the amount of the total output we lose, moreover, one of the most valuable single facts determinable from the examination of the urine.

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2. Collection and Preservation of the Urine

In collecting a 24-hour specimen it is customary to start just before the breakfast hour, for instance at 7 A. M. The patient is instructed to empty his bladder a few minutes before this time and all urine passed thereafter is saved in a clean half-gallon or gallon bottle. The need of voiding immediately before defecation should be pointed out to the patient as an aid in avoiding the loss of some of the urine by admixture with the feces. Just before 7 A. M. on the following morning the patient should again

empty his bladder and complete the specimen with this last voiding. The reason for choosing the 7 A. M. to 7 A. M. period is so that the last meal of the day chosen may have the longest possible period in which to exert its influence on the output of the urinary constituents; and so that for the same reason the specimen may be affected as little as possible by the diet of the previous day.

Unless special methods of preservation are employed urine will upon standing undergo various changes due to bacterial action. Of these the commonest is the so-called *ammoniacal fermentation* due to the decomposition of urea in which ammonia is set free. By the consequent change, in the reaction, in the amounts of urea and ammonia, and in the morphological elements, much of the value of the specimen is lost.

The first essential in the preservation of the urine is a clean bottle, well stoppered. In many hospitals it is customary to sterilize the bottles before use; in private practice the bottle might be boiled. When feasible the specimen should be kept constantly at a low temperature. In hospitals with a refrigerating system cold cupboards may be provided in the service rooms attached to the wards and in the laboratory. The routine use of a preservative in the urine will further ensure its proper preservation and is both simple and efficient. Toluol (10 c.c. to 1 liter) is the most satisfactory preservative. It has no influence upon the chemical tests. Since it floats upon the surface, the urine may not be poured but must be pipetted off for examination. Chloroform may be used but acts as a reducing body and must be removed by boiling before the sugar test is performed.

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B. Physical Methods of Examining the Urine

Physical methods have long been regarded as important in the examination of the urine, but in recent years, coincident with the growth of

physical chemistry, a number of new methods have come into use. For the application of physical chemistry to the study of the urine the following references may be found useful.

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1. Amount of Urine Passed in Twenty-four Hours

(*a*) *Normal Quantity*

In healthy men, this varies between 1,000 and 1,500 c.c., and in healthy women, between 900 and 1,200 c.c. If the quantity be less than 500 c.c., or more than 2,500 c.c., the condition is usually pathological. Very wide temporary variations may however occur in normal persons, and it is a good rule always to bear in mind the modifying influence exerted on the amount of urine by the conditions affecting the other channels for elimination of water (skin, lungs, and intestines). It is obvious that changes in the amount of fluid ingested (hot or cold weather; muscular exertion) or passed with the feces (diarrhea) will affect the quantity of urine secreted. How radically the urinary output may be temporarily affected will be better understood when we recall that the total amount of fluid lost per day through the lungs is 400-600 c.c. and that the amount lost through the skin as sweat varies from 500 c.c. up to 6,000 c.c. The urine, therefore, does not always play the leading part in the maintenance of the fluid-equilibrium in the body. In general, however, the body adapts itself quickly to new external conditions that disturb the fluid-equilibrium and the total urine returns to the accustomed amounts.

In pathological conditions the state of the kidneys, the circulatory conditions in the body (blood pressure; velocity of flow), and nervous influences, play an important part in determining the amount of urine.

(*b*) *Increased Quantity* (*Polyuria*)

Permanent increase in the quantity (*polyuria*) is seen in an extreme degree in *diabetes insipidus* (even as much as 9 to 20 liters may be passed). Polyuria may likewise be very marked in *diabetes mellitus* where it is probably to be regarded as due to the dehydrating properties of the glucose in the blood. In the various *nephropathies,* polyuria is most constant in the chronic interstitial form (*contracted kidneys*); it may also be present in chronic parenchymatous nephritis and in amyloid kidneys. Recovery from acute nephritis is often signalized by a temporary polyuria.

Among the most common clinical types of polyuria is that accompanying the *resorption of edema and of transudates.* This is especially well seen in the stage of recovery from circulatory insufficiency.

In various pathological *nervous conditions,* polyuria is present. In organic nervous disease it may be permanent; while in functional conditions it is more usually transient. It has been assumed that these nervous polyurias are caused by means of the vasomotor control of the renal circulation, but the demonstration of nerve endings in the renal epithelium makes it possible that a direct secretory stimulation occurs. Psychic disturbances, worry, strain, etc., when acute, may be accompanied by a profuse but transient polyuria. The same is true of the onset of certain types of migraine. The *urina spastica* of hysterics is another instance of a functional nervous polyuria. Organic cerebral disease, especially cerebral syphilis, hypophyseal disturbances, etc., may be accompanied by a marked and comparatively permanent polyuria.

The *excretion of toxic bodies* is accompanied by polyuria, that is, these toxic substances are diluted for excretion, so as to be less harmful to the renal epithelium. This principle explains the diuretic action of certain drugs (*e. g.,* calomel, theocin, caffein). The necessity of excreting the toxic bodies formed during the febrile period has been put forward as the cause of the so-called *epicritic polyuria* that often signalizes convalescence in some fevers (especially pneumonia).

(*c*) *Diminished Quantity* (*Oliguria*)

A diminution in the twenty-four-hour quantity (oliguria) is met with in *fever,* in *gout,* in severe *diarrheas* (cholera, exophthalmic goiter), after repeated *vomiting* and during the formation of *edema* or *transudates.* Of the greatest clinical importance are the forms of oliguria occurring in acute and chronic *nephritis.* The total urine in *acute nephritis* is reduced in amount—and the extent of this reduction from day to day is of great value in forming a prognosis. Oliguria is frequent in *chronic parenchymatous nephritis;* while in the chronic interstitial form its appearance is not so usual and is suggestive of an oncoming uremia. Marked oliguria is the rule in *uremic* conditions. Myocardial insufficiency leads to *chronic*

passive congestion of the kidneys, and to marked diminution of the urinary output. Here again the urinary output is in very direct relationship with the functional efficiency of an internal organ of the body and furnishes us, in uncomplicated cases, with valuable data as to the severity and as to the course of the disease.

(*d*) *Anuria*

Anuria, complete suppression of the urine, is due to disturbances in the secretion of urine or in its outflow. *Acute nephritis* leads frequently to anuria, especially the peracute forms seen sometimes following scarlet fever or the ingestion of certain poisons (*e. g.,* arsenic, sublimate of mercury, oxalate, phosphorus) or in eclampsia. Complete anuria is less common in the forms of uremia occurring in contracted kidney. Temporary suppression of the secretion of urine may be caused by a nervous *reflex action* (*e. g.,* following ureteral catheterization, or operative removal of one kidney). Ureteral calculi, ureteral obstruction by tumor masses (*e. g.,* pelvic tumors), operative ligation of the ureters during hysterectomy, all cause obstructive anuria. When the obstruction is below the bladder (urethral stricture, disturbance of the sphincter reflexes) so that though urine may be secreted, it is not voided and the bladder becomes distended, the condition is described by the phrase *retention of urine.*

(*e*) *Pollakiuria; Olikaguria; Dysuria; Nocturia*

Increase and decrease of the twenty-four-hour amount should not be confused with *pollakiuria,* a term applied to the frequent passage of urine (*e. g.,* every half hour, as in cystitis), or with *olikaguria,* in which the bladder is emptied at very long intervals, once or twice a day (*e. g.,* in some cases of tabes). When urination is difficult we speak of *dysuria* or *strangury.*

Aside from variations in the total urine, changes may occur in the *relative amounts of the day and night urines.* The total day urine is usually about double the total of the night voidings. In cardiac and renal disease, however, this relation may be reversed. To this phenomenon of increased night urination the term *nocturia is* applied.

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2. Specific Gravity of the Urine

The specific gravity of the urine is dependent upon the concentration of dissolved substances in the urine. It is thus evidently dependent upon the amount of total urine and upon the amount of total solids excreted. The excretion of these substances is not uniform but follows a curve influenced by diet, exercise, external temperature, etc. The total 24-hour urine alone gives an idea of the average specific gravity. For this purpose determinations on single specimens are worthless.

Normally, in the 24-hour specimen the specific gravity varies between 1.012 and 1.030, though the variations in single portions passed during the day or night may be much wider (1.003-1.040). In pathological conditions the specific gravity of the mixed 24-hour specimen may vary anywhere between 1.002 and 1.040.

Technic.—The specific gravity is determined by immersing a dry aerometer (urinometer) in the urine cooled to the room temperature. One should avoid froth, and see that the instrument swims free. With the eye at the level of the top of the fluid, the mark corresponding to the lower margin of the meniscus of the fluid is noted. The figure 1.000 (or 1,000) on the scale corresponds to the specific gravity of distilled water at room temperature. More accurate determinations of the specific gravity may be made, when necessary, by the use of gravimetric methods (pyknometer); for details as to the use of this instrument larger handbooks may be consulted.

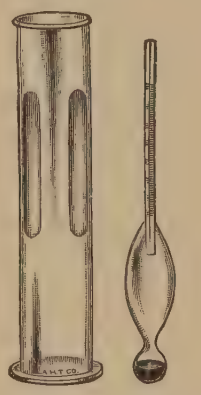

Fig. 431.—Urinometer (Squibb), Graduated from 1.000 to 1.060. (By courtesy of A. H. Thomas Co., Phila.)

The specific gravity depends upon the weight of the substances in solution in the urine. It thus gives us a clew regarding the concentration of the solution. The total weight of the urinary solids passed daily is normally fairly constant, though the total amount of urine is subject to considerable variations. Obviously, therefore, under normal conditions an increased amount of urine is associated with a low specific gravity and *vice versa*.

As a rule the amount of urine varies inversely with the intensity of its color, the specific gravity and the acidity; thus, the more abundant the urine, the paler it is, the lower its specific gravity, and the feebler its acidity. In pathological cases there are two marked exceptions to this general rule:

1. In **diabetes mellitus**, though the amount is large and the color pale, the specific gravity is high (1.030-1.040), owing to the sugar in the urine; and

2. In **severe forms of nephritis** with threatened uremia, the color may be very dark, though the specific gravity may be low, owing to reduc-

tion of the output of salts and urea. This change in the reciprocal relations of specific gravity and color may, however, be masked by the presence of albumin, which increases the specific gravity; in such cases the determination of the molecular concentration of the urine (cryoscopy) (*q. v.*) will give a clew as to the relative amounts of salts and urea present.

The healthy kidney can adapt itself quickly to varying excretory needs. In renal disease, however, both acute and chronic, the kidneys may lose this power of adaptation to varying circumstances. Thus, copious drinking may not be followed promptly by increase in the amount and lowering of the specific gravity of the urine (the excretion of the extra water is delayed (*bradyuria*) and may be incomplete). Still more important is the inability of the kidney in many cases to secrete a concentrated urine rich in urea and salts, and accordingly the 24-hour urine is always of a lower specific gravity than normal (*hyposthenuria*). In Part X the method of distinguishing a hyposthenuria of tubular from one of vascular origin (according to Schlayer) will be described. In hyposthenuria, if the amount of urine be large, the waste products may be eliminated fairly well (*e. g.*, in contracted kidney). If, however, the amount of urine be small, then water and waste products may be insufficiently eliminated, with resulting edema and uremia (*e. g.*, some forms of acute nephritis; chronic glomerulotubular nephropathies).

Marked hyposthenuria is often seen outside of disease of the kidneys themselves (*e. g.*, in pyelitis and in diabetes insipidus).

In urines containing no pathological constituents, an approximate idea of the amount of solids dissolved in the urine may be obtained by multiplying the last two figures of the specific gravity by 2.33 (Haeser's coefficient), the result being the amount of solids in grams in one liter of the urine.

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3. Cryoscopy of the Urine; Determination of the Lowering of the Freezing Point; Mole-Ion Content

In normal urine, the specific gravity bears a definite relation to the excretion of protein end-products and inorganic salts, since these make

up the bulk of the total solids; but in albuminuria and glucosuria, where the weight of albumin and sugar make up an unknown fraction of the total solids, the specific gravity loses some of this significance. Since in renal disease there are often anomalies in the excretion of protein end-products and of salts, some measure of this excretion (to replace specific gravity) has been sought in cryoscopy (*i. e.*, determination of the lowering of the freezing point). The freezing point of a solution is dependent upon the total number of molecules and ions present in it (*i. e.*, upon its osmotic pressure). Colloids such as the protein molecules in solution exert very slight osmotic pressure because their huge molecules are very few in number per unit of weight compared to the great number of relatively minute molecules and ions of the crystalloids. In albuminous urine, therefore, as well as in normal urine, the lowering of the freezing point (indicated by the symbol $\triangle$) will be proportional to the amount of protein end-products and of inorganic salts excreted, the influence of the albumin molecules being negligible. In normal urines $\triangle = 1.0–2.5$; that is, the urine freezes at $-1.0°$ to $-2.5°$ C. In the forms of renal disease in which the concentration of salts and urea is less, the freezing point is not lowered so much ($\triangle = 0.3–0.7$).

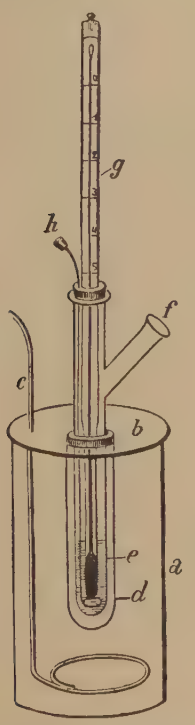

Fig. 432. — Freezing-point Apparatus (Cryoscopy). (After Beckmann-Heidenhain in H. Sahli's "Lehrb. d. klin. Untersuchungs - Methoden," published by F. Deuticke. Leipzig.)

The lowering of the freezing point of the *blood* is usually designated by the Greek letter **δ**. Normally it lies at about -0.56 and shows very slight variation. In uremic intoxication, the freezing point of the blood may be very much lower; the reading being -0.7 or even lower, due, supposedly, to the accumulation in the blood plasma of salts, urea, and other waste products. On this basis, cryscopy of the urine and blood is employed as a functional test of renal efficiency (See Part X). The results obtained show many discrepancies, however, and in this country the method has been largely supplanted by other technically simpler tests.

The lowering of the freezing point is determined by means of Beckmann's apparatus. For clinical purposes, we may use Asher's modification of it, or the cryoscope of Dekhuysen. A test tube containing urine is placed in a freezing mixture (ice and salt) and its contents continually stirred by a platinum stirrer worked mechanically, while the temperature on a delicate thermometer immersed in the urine is watched. The temperature sinks gradually to a point below the freezing point of the urine (over-cooling); then suddenly freezing occurs and the mercury rises quickly to remain stationary at one spot, which is the freezing point of the fluid under examination. One must

make sure that the zero point of the thermometer is controlled by the freezing of distilled water. For the details of cryoscopy the original papers should be consulted.

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4. Electrical Conductivity of the Urine; Ion-content

The electrical conductivity of the urine is due to its content in electrically charged ions. Since these ions result chiefly from the dissociation of certain crystalloid bodies (especially salts), and only to a negligible extent from the colloidal molecules, it is evident that a measure of the electrical conductivity of the urine is an indirect way of measuring its content in dissociable crystalloids. A comparison of such measurements in various urines enables us to note the degree to which the kidneys are retaining or excreting the dissociable crystalloids (See Renal Function, Part X).

The measurement of conductivity in solutions is based on the principle that the resistance of the solution is in inverse proportion to its conductivity. The resistance to the current in passage through the solution is measured by comparison with a known resistance (Wheatstone bridge). The measurement can be rapidly carried out and requires only 1 c.c. of urine. The value of such measurements to the clinician is as yet slight.

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5. Reaction of the Urine

(a) *The Acid-base Equilibrium in the Body*

The reaction of normal urine is usually feebly acid to litmus paper. The degree of acidity is not constant, however, and fluctuations between a feebly alkaline and a distinctly acid reaction occur in the normal person. These fluctuations are due to the part that the urinary secretion plays in the maintenance within the body fluids and protoplasm of the feebly alkaline reaction necessary to the vital chemical and ferment activities. The mechanism that maintains this reaction consists essentially in processes of neutralization and burning of acids in the blood plasma and tissues of the body, and in processes of excretion of acids or alkalis. Such excretion takes place chiefly through the expired air, the urine, the acid gastric juice, and the sweat.

It is chiefly acids of dietetic and metabolic origin that threaten the feebly alkaline equilibrium. The aggression of mineral acids, and of such organic acids as cannot be burned (*i. e.*, especially acids of the aromatic series) is met chiefly by direct combination with ammonium derived from the deaminization of amino-acids. To a lesser extent, the fixed alkaline metals of the body, Na, K, etc., are also drawn upon to meet the acid aggression by the formation of neutral salts. The ammonium salts excreted in the urine represent the results of this type of defense of the body reaction, and the ammonia output is, therefore, a measure of this type of acidosis. On the other hand, organic acids that are susceptible of oxidation (chiefly those of the fatty series) are burned. The carbonic acid formed by this and other physiological oxidations is the source of a constant acid tendency in the body. This acid tendency is met chiefly by the equally constant excretion of CO_2 in the expired air.

The urine and the gastric juice are, however, constant outflows for excess of acid (hydrogen ions). In the more intimate mechanism of the excretion of the $\overset{+}{H}$-ions, the protein molecule, with its ability to fix, and later to free, both $\overset{+}{H}$ and $\overline{OH}$ in accordance with its amphoteric nature, undoubtedly plays an important part. The more recent hypothesis (Hoppe-Seyler, Sertoli, Zuntz), figures the CO_2-excretion in the lung as resulting from the interaction of protein-bound H-ions with the bicarbonate of the plasma.

$$\text{H-protein} + NaHCO_3 + \leftrightharpoons \text{Na-protein} + H_2O + CO_2$$

In the elimination through the kidneys of the excess of H-ions, it is probably the acid protein molecule reacting with neutral disodium phosphate that gives rise to the acid monosodium phosphate that is excreted.

$$\text{H-protein} + Na_2HPO_4 \rightleftarrows \text{Na-protein} + NaH_2PO$$

By this reaction, one-half of the sodium involved is saved to the body, while an equivalent amount of H-ions is excreted. This excretion of acid monosodium phosphate is usually the chief cause of the acidity of normal urine. When the alkaline equilibrium in the body does not require the excretion of H-ions, a greater proportion of the neutral disodium phosphate, Na_2HPO_4, may appear in the urine, and when the balance inclines in the body to the alkaline side, the alkaline trinatrium phosphate, Na_3PO_4, may be excreted in quantities sufficient to give to the urine an alkaline reaction.

(*b*) *Factors in the Acidity of the Urine*

While quantitative studies have usually shown that the reaction of the urine is determined by the acid phosphates, it is of course contributed to by all the acids in the urine proportionately to their concentration and to their degree of ionic dissociation. Henderson states that, on theoretical grounds, it seems certain that all acids having a dissociation-constant greater than 10^{-4} (such as HCl, H_2SO_4 and oxalic acid) are present in the urine entirely in the shape of their neutral salts; acids with a dissociation-constant equal to 10^{-4} (hippuric acid, lactic acid) are 98-99 per cent in the form of neutral salts; acids with a dissociation-constant 10^{-5} (β-oxybutyric acid) are eliminated $\frac{3}{4}$ as neutral salts and $\frac{1}{4}$ as free acid; acids with a dissociation-constant 10^{-6} (uric acid) are eliminated $\frac{1}{4}$ as neutral salt and $\frac{3}{4}$ as free acid; and, lastly, all acids with a dissociation-constant of 10^{-7} (carbonic acid, mononatrium phosphate) or less are excreted almost entirely in the form of free acid.

A more direct demonstration of the importance of other factors in the urinary acidity besides the acid phosphates has been furnished by the work of Folin and Dresers who have shown that the total titratable acidity of the urine is frequently greater than can be explained by assuming that the total phosphate-content is in the form of acid phosphate. They infer that the remaining acidity is due to free organic acids. This organic acid quotient, Folin states, may equal at times one-half of the total titratable acidity. Moreover it is certain that under pathological conditions in which acidoses occur, a disproportionate excretion of certain acid bodies occurs in the urine the reaction of which may then, for the time, be determined by these bodies. In the types of acidosis, for instance, due to a defect in fat catabolism (acidosis of diabetes, of starvation, of certain febrile conditions) the ketonic acids, β-oxybutyric, and aceto-acetic acids, are excreted in tremendous amounts and the moiety present in the urine in the form of free acid exerts a controlling influence on its reaction. The excretion of uric acid at the onset of an attack of gouty arthritis may rise to a

point where it dominates the urinary reaction. Therapeutically administered, mineral and aromatic acids escape combustion in the body, and appear in the urine partly at least in the form of free acid. By their means an alkaline urine may be rendered acid. There are also unknown acids to be considered, present in certain as yet little understood acidoses. Sellards has described acidoses in renal diseases in which an unknown acid body was excreted. Magnus Levy has mentioned the occurrence of an unknown acid excreted occasionally in connection with β-oxybutyric acid in amounts up to 10 per cent.

Aside from these pathological types of acid excretion, urinary superacidity may be found as a compensatory process when the acid secretion from the stomach is diminished (gastric subacidity), or when, on the other hand, there has been a large drain upon the alkalis of the tissues as in the formation of large exudates of alkaline reaction or in the outpouring of intestinal secretions in cholera. Simple acceleration of the metabolic processes leading to acid formation, heavy protein diet, severe muscular exertion, or febrile conditions will be accompanied by increased acidity of the urine.

(*c*) *Measurements of the Acidity of the Urine*

The measurement of urinary acidity presents somewhat the same problem as is offered by the blood serum. The actual reaction, that is the concentration of $\overset{+}{H}$ and $\overline{OH}$ in terms of gram anions and gram kations, constitutes a difficult physicochemical problem, the results of which are as yet of little clinical utility. The total potential acidity, that is the total of the $\overset{+}{H}$-ions that will be formed in the face of a continued neutralization of those in the solution, may be approximately determined by simple titration methods. The results obtained by titration of the urine with an alkali, *e. g.*, N/10 NaOH, will depend upon the indicator. Phenolphthalein reacts to all bodies of an acid nature, but in the presence of calcium and ammonium salts the figures obtained are not reliable. Folin has overcome this difficulty by adding potassium oxalate to the urine. In this way, both the di- and tri-calcium phosphates are held in solution and the hydrolysis of the ammonium compounds becomes negligible.

i. Folin's Method of Determining the Total Acidity of the Urine

1. With a pipet, place 25 c.c. of urine, from the carefully preserved 24-hour specimen, into a 200 c.c. Erlenmeyer flask.
2. Add one or two drops of phenolphthalein (0.5 per cent phenolphthalein in 50 per cent alcohol).
3. Add 15–20 gms. of powdered neutral potassium oxalate. Shake one minute.
4. Then titrate, *at once,* with $\frac{N}{10}$ NaOH until a faint, yet distinct, pink color-

ation is produced throughout the contents of the flask. Shaking should be continued throughout the titration, so as to keep the solution as strong as possible in oxalate.

The results may be expressed in acidity per cent in terms of $\frac{N}{10}$ NaOH by multiplying by four. Normal values with this method are 25–30 acidity per cent. (Wood.)

If it be desired to study the *partition* of this total acidity in its organic and inorganic components, special methods must be employed. For all ordinary studies of the acidity of the urine, a sufficiently accurate idea of this partition may be obtained by determining the total phosphates by the uranium nitrate method. Seven and one one-hundredth mg. of P_2O_5 have an acidimetric value equal to 1 c.c. of tenth-normal acid. The acidimetric value of the total phosphates may be assumed to approximate total inorganic acidity. Hence if the total titratable acidity is distinctly greater than the calculated acidimetric value for the phosphates, the excess may be taken to be due to free organic acids. (Folin.)

(*d*) *Alkaline Urines*

Whereas, the observations upon the degree of acidity of an *acid urine* draw their interest from the indices they furnish us of the relationships between the urinary ingredients and the metabolism of the body as a whole, our interest in the presence of an *alkaline urine* is more based upon the evidence this may yield of the presence of pathological conditions in the genito-urinary tract. It is, however, true that the same attempt of the body plasma and protoplasm to maintain a *feebly* alkaline reaction, which in the event of over-production of acid leads to the secretion of a hyperacid urine, will, in the presence of an excess of alkali, lead to the elimination of an alkaline urine. The phosphates will be excreted in the form of Na_2HPO_4, or even of Na_3PO_4.

Such amphoteric, or even alkaline, urines may be found in persons on a vegetable diet (the acetates, tartrates, citrates, etc., of fruits and vegetables being burned to alkaline carbonates and rendering the urine alkaline). Therapeutic administration of the citrates, of tartrates, and of sodium bicarbonate will, likewise, alkalinize the urine. The rapid absorption of exudates and transudates (always alkaline in reaction) neutralizes the urine. Gastric supersecretion or gastric superacidity result in a diminution in the acidity of the urine, or in the secretion of an alkaline urine. In all such urines, the reaction is due to fixed, *i. e.*, non-volatile, alkalis.

More diagnostic interest attaches to another class of cases, in which an alkaline urine is voided, the reaction of which is wholly dependent on local conditions in the genito-urinary tract. The so-called "ammoniacal decomposition" of the urine in certain cases of cystitis results in a strongly alkaline urine in which the reaction is due, not to fixed alkali, but to volatile ammonium salts. These salts, ammonium carbamate and carbonate, are formed from urea by the action of certain bacteria (*Micrococcus ureae*). The urea, with the addition of water, forms ammonium carbonate,

$$CO(NH_2)_2 + 2H_2O = (NH_4)_2CO_3$$

Ammonium carbonate is unstable; it goes over in part into ammonium carbamate:

$$(NH_4)_2CO_3 = H_2O + NH_2 \cdot COONH_4$$

and in part is dissociated into carbon dioxid, ammonia and water:

$$(NH_4)_2CO_3 = CO_2 + 2NH_3 + H_2O$$

Freshly voided urine showing volatile alkalinity is of diagnostic significance as to the presence of infection of the urinary tract.

Ammoniacal decomposition of urine occurs in almost all urines after voiding unless precautions are taken to prevent bacterial growth. No stress, therefore, can be laid upon any determination of urinary reaction unless the specimen is one either freshly voided, or that has been carefully preserved.

The ammoniacal odor will often be sufficient to distinguish the urine the alkaline reaction of which is due to volatile alkalis from that in which the fixed alkalis are responsible. A glass rod moistened with HCl and held over such an ammoniacal urine gives rise to white clouds of ammonium chlorid vapor. A piece of red litmus paper moistened with ammoniacal urine turns blue, but, on drying in the air, the blue color disappears; if the alkalinity of the urine be due to fixed alkali and not to ammonia, the blue color will persist on drying.

(e) *Relations of the Reaction of the Urine to Sediments in the Urine*

The type of sediment in the urine is affected by its reaction. In acid urines a brick dust sediment of urates (*sedimentum lateritium*) often appears, especially on cooling. It dissolves when the urine is heated or when NaOH is added.

If the urinary acidity be excessive, uric acid may be set free from its salts and be precipitated from the urine in whetstone-shaped crystals along with envelope-shaped crystals of calcium oxalate. As soon as the reaction of the urine becomes amphoteric, alkaline earthy phosphates, and, sometimes, earthy carbonates, are precipitated as a whitish sediment. Such phosphatic precipitates dissolve immediately upon the addition of acetic acid (contrast with precipitate due to albumin), but are unaltered by the addition of NaOH. The sediment of the strongly alkaline ammoniacal urines contains coffin-lid crystals of triple phosphates $(NH_4)MgPO_4$ and thorn-apple crystals of ammonium urate.

If there be a pyuria the pus will vary in appearance, according as the urine is acid or alkaline; when acid, the pus will have a crumbly appearance, while when alkaline it will settle in sticky mucoid strands.

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6. Color of the Urine

The yellow color of normal urine is lighter or darker according to the concentration of the urine in the normal pigments (chiefly urochrome, uroerythrin, urobilin). It varies from almost water clear urine to urine of a reddish brown color. In the spectroscope normal urine gives no characteristic absorption spectrum. Most normal urines show a slight degree of fluorescence.

In normal persons the total excretion of urinary pigments is fairly constant and accordingly the depth of color depends chiefly upon factors governing the water output (fluid ingestion, muscular exercise, external temperature, etc.)

The color of the urine in certain diseases is likewise due chiefly to disturbances in the water output. In the oliguria of cardiac disease and of febrile processes the urine is high colored (yellowish red or brownish red); while a characteristic pale urine is voided in the polyuria of diabetes or of contracted kidney. Variations in the excretion of the normal pigments also affect the color of the urine in certain diseases. In chlorosis a lack of pigment is the cause of the pale urine; while the high-colored urine in pernicious anemia is the result of excess pigment due to blood destruction.

In other conditions the color of the urine is due to *pathological pigments.* In icterus the excretion of bile pigments (bilirubin, urobilin, biliverdin) give the urine a beer-colored, dark yellowish brown color with yellowish foam. In hematuria and in hemoglobinuria the urine is reddish (meat juice color); it may have a greenish cast, and often presents a *smoky* appearance.

Far rarer than the two preceding common types of abnormal pigment excretion are the cases of melanuria (melanotic tumors), of alkaptonuria (*q. v.*) and of the increased excretion of indican and various phenol derivatives (in marked intestinal putrefaction, gangrene, suppuration). In all these urines a brownish black color appears on standing exposed to the air. In chyluria, due to the excretion of fat, the urine may have a milky appearance or resemble *café au lait.*

In all cases in which the urine is abnormally colored *pigmentation due to medicinal agents* should first be thought of, as a possible cause. A urine the color of claret or port wine is voided in some cases after administration of the hypnotics (sulphonal, trional, tetronal) and is due to the excretion of the iron-free blood-pigment hematoporphyrin. Carbolic acid, guaiacol, creosote, resorcin, naphthalin, salol and various tar preparations may be followed by the voiding of a dark brown to black urine (color deepens on standing), due to the excretion of hydroquinon and pyrocatechin. Methylene blue gives the urine a greenish or blue color. Chrysarobin, senna, rhubarb, and cascara produce a golden yellow urine that assumes a red color upon addition of alkali.

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C. Chemical Methods of Examining the Urine for its Normal Constituents

1. The Normal Constituents of the Urine (Organic and Inorganic)

For practical purposes it is convenient to subdivide the constituents of the urine into those that are normal (physiological) and those that are abnormal (pathological), meaning by the latter those that normally do not occur at all or are present only in traces not recognizable by ordinary tests. The normal constituents are of less diagnostic significance than the pathological, but the demonstration of quantitative changes in the normal constituents is of great importance for the understanding of metabolic processes.

If one liter of normal urine be evaporated to dryness, about 40 grams of *solid residue* will be obtained. If this residue be incinerated about one-third remains as incombustible *ash*. The part that disappears on incineration consists of the *organic substances* made up chiefly of urea and in part of the so-called extractive substances (uric acid, urinary pigments, mucin, etc.). In a person on a mixed diet the most important organic and inorganic constituents in the urine passed during twenty-four hours are the following:

Total Solids (40 to 65 Grams) in One Liter of Normal Urine

Organic Constituents 25 to 40 g.	Inorganic Constituents 15 to 25 g.
Urea 20—35 g.	Sodium Chlorid (NaCl) 8—15 g.
Creatinin 1.0—1.5 g.	Phosphoric Acid (P_2O_5) 2.5—3.5
Uric Acid 0.5—1.25	Sulphuric Acid (SO_3) 2—2.5
Hippuric Acid 0.1—0.7	Potassium (K_2O) 2—3
Other Constituents (Ethereal Sulphates, Oxalic Acid, Urinary Pigments, etc., 1.5—2.3 g.	Sodium (Na_2O) 4—6
	Calcium (CaO) 0.1—0.3
	Magnesium (MgO) 0.2—0.5
	Ammonia (NH_3) 0.3—1.2
	Iron (in Pigment) 0.001—0.010

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2. The Nitrogenous Constituents of the Normal Urine

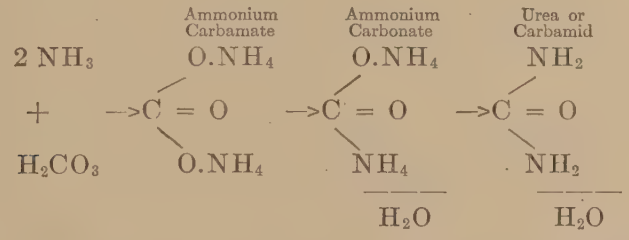
(a) *Sources of the Nitrogenous Substances of Normal Urine*

The bulk of the organic substances of the urine is made up of bodies containing nitrogen. These are derivatives, by direct or indirect paths, of protein metabolism. Protein, which is essential to the building of body protoplasm, besides C, H, and O, constantly contains N. Moreover, the non-protein nitrogen is so small in amount that for practical purposes nitrogenous metabolism is equivalent to protein metabolism.

Protein of food is broken down by the digestive juices into its constituent amino-acids. These cleavage-products, resorbed through the intestinal wall, are resynthesized, chiefly at this point, to form body proteins. A certain amount of these is necessary for the formation of tissue protoplasm. The amount in excess of this need is split to amino-acids; the catabolism of the protein constituents of the tissue cells likewise results in the production of amino-acids. The amino-acids from both these sources suffer deamination probably in the liver, or possibly in the intestinal wall.

$$\begin{array}{l} R \\ | \\ CHNH_2 \\ | \\ COOH \end{array} + H_2O = \begin{array}{l} R \\ | \\ CHOH \\ | \\ COOH \end{array} + NH_3$$

The remnant of the amino-acid then undergoes oxidative processes, resulting in CO_2 and H_2O. The NH_3-groups in part form ammonium salts of the free acids in the blood, and in much greater proportion unite with H_2CO_3 of the blood to form urea.



Urea and *ammonium salts* form thus the chief nitrogenous end-products of protein metabolism.

There are, however, bodies produced in the metabolism of tissue proteins, the catabolism of which results in nitrogenous end-products distinct from urea and ammonium salts. Such a body, *creatin,* is found in muscle-plasma, the product of muscle-cell metabolism; it is changed to

urea only to a slight extent; for the most part it is excreted in the urine as its anhydrid *creatinin.*

Similarly, nucleoproteins of the food and of the body tissue contain in their nucleic acid fraction a characteristic chemical group called *purin.* When these purin groups are set free by the hydrolytic cleavages of intestinal digestion and resorption, or of tissue catabolism in the body, they undergo, for the most part, oxidation to trioxypurin, *i. e., uric acid.* Methylpurins are, however, excreted as such. A fraction of the uric acid is transformed into urea, but the greater part is excreted as uric acid in the urine.

The chief organic constituents of the urine, therefore, are: (1) *urea* and *ammonia,* which are the usual end-products of protein metabolism; (2) *creatinin,* which is a result of a distinctive metabolic process in muscle tissue; (3) *uric acid* and other *purins,* which are the end-products of a characteristic metabolic process in cell nuclei of the body tissues (endogenous purin) or of digestion of nucleoproteins in the diet.

If the nitrogen contained in these constituents of the urine be subtracted from the total nitrogen of the urine the difference is called the *undetermined nitrogen.* This fraction is due to the presence of small amounts of a great number of nitrogenous bodies. For the most part these are protein split-products: conjugated amino-acids, *e. g.,* hippuric acid; traces of free amino-acids; amins and diamins; polypeptidlike substances (*e. g.,* oxyproteic acids). In this fraction also fall the normal urinary pigments (urobilin, urochrome, uroerythrin (*q. v.*), and other even less defined nitrogenous compounds.

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(*b*) *The Total Nitrogen of the Urine and Its Relation to the Nitrogen Balance of the Organisms*

Valuable data as to protein metabolism are obtained by comparison of the nitrogen intake with the nitrogen output; that is, by determining the nitrogen balance of the body. For this purpose the amount of nitrogen in the food (minus that lost in the feces) is compared with the nitrogen output in the urine. In special cases the output in the sweat, the sputum, etc., must also be considered. (For full details, see Part XIII).

In normal cases the protein metabolism adjusts itself in such wise that the nitrogenous intake is equal to the nitrogenous output, that is,

the body is in *nitrogenous equilibrium.* Reduction of the protein intake below a certain point is accompanied by a nitrogen deficit, that is, the excretion of nitrogen is greater than the intake. Tissue protein is replacing dietetic protein. If the withdrawal of all protein from the diet be accompanied by the ingestion of sufficient fats and carbohydrates to meet the caloric requirements of the body the catabolism of tissue protein is much less than in complete starvation. Fats and carbohydrates are protein sparers. It is found, therefore, that the body can maintain nitrogenous equilibrium upon the smallest amount of protein when the diet is rich in fats and carbohydrates.

The amount of the minimum requirement in protein varies in different persons. Chittenden's work has shown that a daily protein intake yielding 5-6 gram total nitrogen in the urine will satisfy the body requirements. The amount of total nitrogen in the urine under the usual mixed diet varies between 10 and 16 grams a day.

Protein ingested in excess of the body's need is burned. Protein storage in healthy men of normal weight does not occur except during the period of growth. In pathological conditions a similar retention of nitrogen occurs in convalescence from febrile diseases, following periods of undernutrition, during the period of formation of exudates, in pregnancy, etc. In these cases the nitrogen intake exceeds the nitrogen output, that is, the N balance is positive.

The N balance, on the other hand, is negative in all conditions of pathological undernutrition. In such conditions serum protein and muscle protein are burned. Similarly the resorption of protein-containing exudates is followed by destruction of this protein and the elimination of large amounts of nitrogen in the urine (*e. g.,* the epicritic nitrogen elimination in pneumonia).

Another type of protein destruction in the body is that due directly to the cause of the disease. Of this type the most marked instance is found in exophthalmic goiter. The general heightening of oxidative processes in these cases is accompanied by a marked burning of tissue protein and a consequent negative N balance. In fevers, similarly, the nitrogen elimination is increased. It is improbable that this is due to the increased temperature *per se,* as no parallelism between N excretion and the height of the fever is discoverable. In the rare cases of typhoid fever that run their course with hypothermia, the wasting is nevertheless marked. In certain diseases (pneumonia) a retention of nitrogen may occur during the febrile stage, to be followed by an epicritical excess elimination.

Other diseases accompanied by excessive N elimination as a result probably of toxic processes, are leukemia, the cachexia of malignant disease and many poisonings (phosphorus, arsenic, chloroform).

Interpretation of studies of the nitrogen equilibrium must be conservative. Many factors are present that are potent in temporarily disturb-

ing this equilibrium. The excretion of nitrogenous end-products usually occurs quite promptly (*e. g.*, the curve of excretion of urea reaches its height about 7 hours after the ingestion of the protein food); but in some instances an inexplicable lag in the appearance of these products occurs, so that it is only by averaging the intake and output for many days that nitrogen equilibrium is shown to exist. Inferences based on a single day in such a period would evidently be open to error. The drinking of large amounts of water is usually followed by a temporary rise in the urinary nitrogen, which is apparently due to washing out of nitrogenous end-products. The fluid intake must therefore be carefully controlled.

A very important influence affecting the nitrogen output in the urine lies in the degree of functional ability of the kidneys to excrete the nitrogenous bodies. (See Renal Functional Tests, Part X.) In general the chronic nephropathies tend to show disturbances of this renal function; and it is to a high grade retention of this sort that the uremic intoxication has commonly been attributed. Such a factor in the nitrogen elimination must of course be ruled out before conclusions as to protein metabolism can be drawn.

Total nitrogen is determined by the same method in the urine, the feces and in foodstuffs.

(c) *Determination of the Total Nitrogen According to Kjeldahl*[181]

Principle.—The principle involved is the transformation of the nitrogen in the nitrogenous bodies of the urine into ammonia and thence into ammonium sulphate by heating with H_2SO_4 in the presence of a catalyser. The ammonium sulphate formed is then decomposed by strong NaOH. As ammonia becomes free, it is driven over into a receiving vessel containing a known amount of N/10- or N/4-H_2SO_4 (which is thereby partially neutralized). The extent of this neutralization is determined by titrating the remaining acid with standard alkali solution (N/10-NaOH).

Technic.—For carrying out such a determination, we need (1) concentrated H_2SO_4 (free from N), (2) pure crystals of $CuSO_4$, (3) pure potassium sulphate, (4) 40 per cent NaOH (free from HNO_3), (5) talc powder, (6) N/10-sulphuric acid, (7) N/10-sodium hydrate. All reagents should be N-free. As an indicator in the titration, a solution of rosolic acid is used (6.5 grams pure rosolic acid plus 50 c.c. dilute alcohol plus 50 c.c. water), or alizarin, 1 per cent solution, or buteol, 0.2 per cent alkaline solution, or, perhaps best of all, tincture of cochineal (filtrate from cochineal bugs ground in 50 per cent alcohol).

The amount of urine used is 5 c.c. (if the concentration of the urine is low 10 c.c. should be used). The measurement must be made exactly by means of a pipet. The urine is placed in a Kjeldahl flask, and 10–15 c.c. of concentrated H_2SO_4 added. The urine immediately turns brown. We now add a piece of pure $CuSO_4$ the size of a pea, and 5 grams of potassium sulphate. The flask is then heated under a hood. Heating must be very gentle at first until foaming has

ceased, after which the fluid can be kept actively boiling. One must make sure that no black spots remain on the walls of the flask (unburnt substance). If any persist, they must be washed down by carefully shaking the flask. When the fluid is colorless, or a constant pale green color, heating is stopped, and the flask is allowed to cool. When cool, the neck of the flask is washed with distilled water so that all traces of material are carried back into the body of the flask.

The contents of the Kjeldahl flask are now diluted with 200 c.c. distilled water, and 120 c.c. of 40 per cent NaOH are added in two separate portions, care being taken not to lose any ammonia (and with it nitrogen). One adds at first only a part of the NaOH, not enough to neutralize the acid, allows this to cool, and adds a spoonful of talcum to prevent violent splashing during the distillation. The remaining NaOH is then poured in quickly and the flask united immediately with the distilling apparatus. The latter consists of a water-cooled condenser provided with a Fresenius bulb or similar device to prevent alkali passing over by spurt-

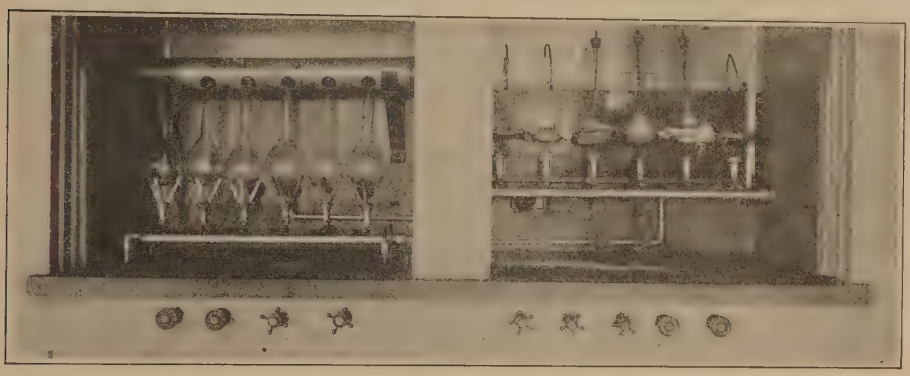

Fig. 433.—Kjeldahl Apparatus for Estimation of Total Nitrogen. The Figure on the Left Shows the Kjeldahl Digesting Rack (Folin Modification) for Simultaneous Oxidation of Six Specimens. That on the Right Shows the Kjeldahl Distilling Apparatus; the Ammonia Is Condensed As It Passes Through the Tubes into the Receptacles Below Containing Acid of Known Concentration.

ing. The outlet tube passes into an Erlenmeyer flask, which should contain 50 c.c. of N/10-H_2SO_4. The end of the outlet tube must be below the surface of this fluid.

The distillation is now carried on, the flask being heated slowly at first until boiling has become regular. At the end of half an hour the ammonia should be completely driven over, but to be sure, a test of the distillate should be made with red litmus paper. If this still turns blue, the distillation must be continued. The litmus paper used for the test should be washed off into the receiving flask in order to avoid all loss.

When the ammonia has all been driven over the Erlenmeyer flask is lowered until the tube from the cooler is well above the level of the fluid. The distillation is now continued for five minutes longer in order to wash out the whole tube thoroughly with distilled water. The outlet tube is rinsed externally and internally with distilled water into the Erlenmeyer flask. After addition of the indicator (*e. g.*, 4 drops of the tincture of cochineal), the standard acid solution in the Erlenmeyer flask is titrated with N/10-NaOH.

Calculation.—To calculate the N-content one subtracts the number of cubic centimeters of N/10-NaOH used from the number of cubic centimeters of N/10-H_2SO_4 first placed in the receiving vessel, and multiplies the result by 1,401.

This gives the amount of N in milligrams contained in the amount of urine used. Let us assume that the 24-hour quantity of urine amounted to 500 c.c. and that 5 c.c. of this were used for the titration. In the Erlenmeyer flask we placed 50 c.c. N/10-H_2SO_4. On titrating back with N/10-NaOH 15 c.c. were required; in other words, 35 c.c. of N/10-H_2SO_4 had been neutralized by the NH_3 distilled over. The milligrams of N present therefore = 35 x 1,401 = 49,035 mgr. The total amount of nitrogen in the 500 c.c. would then amount to 4.9035 grams.

Application to Feces.—The total nitrogen of feces can be estimated in a similar way. After a little H_2SO_4 has been added to the total amount of feces it is dried to constant weight at 120° C. The mass is then pulverized in a mortar and the powder well mixed. The total amount is weighed and an aliquot portion taken, say 1 gram, and placed in a Kjeldahl flask, after which the titration is the same as for urine. The nitrogen-content of foodstuffs is similarly determined (see larger text-books).

Microchemical Method of Determining Total Nitrogen.—By the micro-Kjeldahl method devised by Folin and Farmer the total nitrogen of the urine, or of the blood, may be determined with the use of only a small amount of material. The method is rapid and accurate enough for clinical use. It is described in the section on the blood (see Part VII).

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(*d*) *The Nitrogen-Partition in the Urine*

The partition of the total nitrogen of the urine among the various nitrogenous bodies, which represent the products of protein metabolism, varies markedly under different conditions. The protein intake is of great importance in affecting this nitrogen partition as is demonstrated in this table of Folin's and Chittenden's.

	Excretion in Grams		Percentage of Total N	
	Mixed Diet	N-Free Diet	Mixed Diet	N-Free Diet
Nitrogen	16.00	3.60	100.00	100.00
Urea N	13.90	2.20	86.87	61.70
Ammonia N	0.70	0.42	4.37	11.30
Creatinin N	0.58	0.60	3.63	17.20
Uric Acid N	0.12	0.09	0.75	2.50
Undetermined N	0.70	0.29	4.37	7.30

From the study of the facts brought out in this table it is evident that the metabolism of endogenous protein is of a different type than that of exogenous protein. The catabolism of endogenous protein yields much less urea, and there is a proportionate percentage increase in the other constituents. Creatinin excretion is seen to remain constant in quantity; the inference is that it is produced in the body at a rate comparatively uninfluenced by the level of protein metabolism. In brief it can be seen that a knowledge of these normal variations of the nitrogen partition lies at the base of any study of the anomalies of protein metabolism in disease. It is only when the interrelationships of all the protein end-products are kept in mind that any deductions may be drawn from the data on the excretion of one of them in the urine.

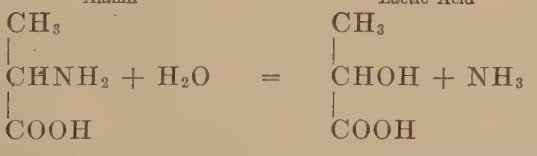
(*e*) *Urea* [$CO(NH_2)_2$]

Urea (often abbreviated as U), $CO\begin{matrix}\diagup NH_2\\ \diagdown NH_2\end{matrix}$, carbamid, is the most important organic constituent of the urine.

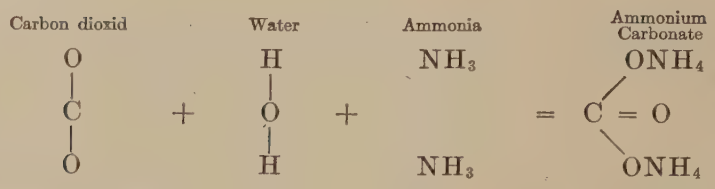
i. Sources of the Urea of the Urine

The *sources* of this urea lie in the endogenous and exogenous protein metabolism. Urea is an end-product of catabolism of the protein, and of the creatinin of the body tissues; and it likewise arises when protein in excess of the body needs is synthesized from the amino-acid end-products of digestion; for this excess protein of exogenous derivation cannot be stored and hence is catabolized. Ammonia, amino acids, and creatinin ingested as such in the food are likewise exogenous sources of urea formation.

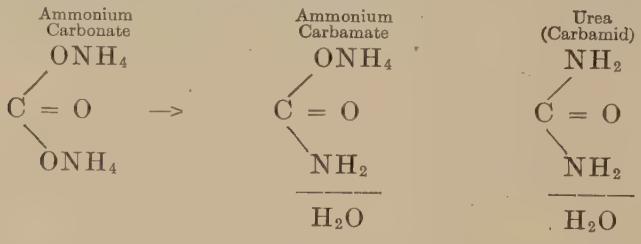
Formation of Urea in the Body.—The *formation of urea* can, in the laboratory, be accomplished by many reactions. In the human body, it is conceded that the greater part of the urea is formed as follows: Amino-acids, resultant of both exogenous and endogenous protein catabolism, undergo deaminization; their NH_2 groups are split off to form NH_3;



the NH_3 combines with CO_2 of the blood to form ammonium carbonate;



and this salt undergoes anhydration to urea, passing through the intermediary stage of ammonium carbamate:



A certain amount of urea (probably small) is also known to be formed in the liver as a result of the action of arginase upon arginin, which by direct cleavage yields urea and ornithin. It is also known that urea is formed from creatinin, but by what reactions is not yet proven. Urea formation takes place chiefly in the liver; but certainly not exclusively in the liver, for apparently normal urea formation has been observed in animals in whom the liver was secluded from the circulation.

Curve of Elimination.—The curve of *urea elimination* following protein ingestion, rises about three hours after the meal, reaches its height about the sixth or seventh hour, and then falls slowly to the base line, which it reaches at from twelve to twenty hours. This curve represents the results of catabolism of the excess protein of exogenous origin. In starvation, on the other hand, the catabolism of endogenous protein results in an elimination of urea, the curve of which is nearly a straight line. On a mixed diet, the more nearly the protein intake approaches the normal protein requirements of the body, the more nearly the curve of urea elimination approaches a straight line.

Relation of the Urea Nitrogen to the Total Nitrogen.—The total nitrogen elimination cannot be deduced from that of urea. The urea fraction of the total nitrogen is variable. In starvation, the catabolism of endogenous protein yields a urea fraction which constitutes only 60 per cent of the total N output. On a mixed diet, however, that is, when catabolism of both exogenous and endogenous protein is taking place, the nitrogen output is 85-90 per cent in the form of urea. It is apparent, therefore, that the nitrogen of protein that is in excess of the body's needs, is excreted almost completely as urea, while only about 60 per cent of the nitrogen of tissue protein appears in this form. The relations of the total

urea and the total nitrogen excretion fluctuate too widely with diet, therefore, to permit of our safely deducing one from the other.

In general, however, urea elimination is increased by the same factors that increase the total nitrogen output; hence the output is greater on a rich meat diet, in febrile conditions, in exophthalmic goiter, in wasting diseases, and in other instances of increased protein catabolism. Like the nitrogen output, we find the urea elimination diminished in periods of growth, in convalescence, on a low protein diet, and during the rapid formation of exudates.

Relation of Urea Nitrogen to Ammonia Nitrogen.—A balance exists naturally between the outputs of ammonia and urea in the urine. In the body, ammonia, formed by the deaminization of amino-acids, is abstracted from the formation of urea in proportion to the quantity of acid bodies present, since these must be neutralized and excreted as ammonium salts. Hence, in acidosis, the ammonia-N percentage increases at the expense of the urea-N percentage, while under therapeutic administration of alkalis, *e. g.*, potassium citrate, the ammonia output is diminished and the urea output increased.

Relation of Urea Elimination to Hepatic Function.—Since urea is formed largely in the liver, especial interest attaches to the influence of disease of this organ upon the urea output. In acute yellow atrophy, cirrhosis, and various pathological processes affecting the parenchyma of the liver, reductions of the urea-N percentage in the urine, with increase of the ammonia-N have been reported. The change is by no means constant, however; and, moreover, the influence of diet and of coincident acidosis have not been sufficiently considered. The formation of urea in other tissues will readily explain the negative results in cases in which liver substance is known to be destroyed.

Relation of Urea Elimination to Renal Function.—Normal kidneys excrete urea rapidly and quantitatively. But in the chronic nephropathies there is often a delayed elimination of the nitrogenous bodies, including urea. It has been held that, in these conditions, a compensatory elimination of urea through the skin and the intestines occurs. Normally, only one-half to two grams of urea are excreted through these paths. It has not been shown by controlled work, however, that in cases of renal retention this amount is significantly increased. This matter will be more fully discussed in Part X, in connection with the determination of the urea-secretory constant of Ambard, and other methods of functional renal diagnosis.

ii. The Quantitative Determination of Urea in the Urine

The chief utilization of determinations of urea in clinical investigations is in connection with the study of metabolism and the study of renal function.

The rapid hypobromite method of determination is not accurate enough. The older methods of Folin, of Mörner-Sjöcvist, and of Benedict are accurate, but are time-consuming and elaborate (cf. larger manuals). Marshall's recent method is simple and accurate.

1. *Marshall's Method for the Determination of Urea*

Principle.—The *principle* of the method consists in the hydrolysis of the urea to ammonium carbonate by the ferment (urease) present in the soya bean. The ammonia of the ammonium carbonate is then determined by Folin's method. The preformed ammonia is subtracted from this value.

Technic.—One part of powdered soya bean is mixed with ten parts of water and allowed to stand one hour at 35° C. The protein contents are then precipitated by the addition of one-tenth the volume of N/10-HCl and removed by filtration. The filtrate is preserved under toluol until required for use.

Into each of two test tubes is introduced exactly 1 c.c. of the urine, measured with an Ostwald pipet, and to each 9 c.c. of water are added. To one of the tubes is now added 1 c.c. of the soya bean extract, and to the contents of each tube 0.5-1 c.c. of toluol are then added. These tubes are then kept over night at room temperature. Two cubic centimeters of a saturated solution of potassium carbonate are then added to each tube, with 2 grams of sodium chlorid, and kerosene oil to prevent foaming. The ammonia formed is then blown over by Folin's method (see Ammonia) into 50 c.c. of N/10-HCl. It is safer to use two absorption flasks. The acid is then titrated with N/10-NaOH, using a few drops of alizarin red as an indicator. In this way, the amount of acid that has combined with the ammonia is determined. One cubic centimeter of N/10-HCl is the equivalent of 0.001401 gram of nitrogen. In the tube to which no urease was added, the N found is that due to preformed ammonia. In the tube in which urease has acted, the nitrogen found is that due to total ammonia, that is, preformed ammonia plus the ammonia derived from urea. Subtracting the nitrogen-value of the preformed ammonia from that of the total ammonia, we have the nitrogen due to urea, and this value, multiplied by 2.143, gives the urea in grams in 1 c.c. of urine.

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(*f*) *Ammonia* (NH_3)

Although in the chemical classification ammonia is included under the inorganic constituents, it will be discussed here because of its close relationship to the other nitrogenous bodies of the urine, of organic origin. The average daily ammonia excretion in the urine, on a mixed diet, is 0.7 gram, the nitrogen of the ammonia making up 4.5 per cent of the total nitrogen.

i. Sources of the Ammonia of the Urine

Relations of NH_3 to Urea and to Total Nitrogen.—Ammonia finds its chief source within the body in the deaminization of amino-acids of both *endogenous* and *exogenous* origin. Some ammonia is absorbed as such from the intestine, derived from ingested ammonium salts, or from the ammonia resulting from bacterial action upon amino acids.

The ammonia present in the body is chiefly in the form of ammonium carbonate. From this salt, urea is formed. An equilibrium no doubt exists between ammonium carbonate and urea, as a consequence of which both salts are constantly present in the blood; hence the excretion of a small amount of ammonia, in the form of ammonium carbonate, may be accounted for. The greater part of the ammonia that is excreted, however, has been abstracted from the ammonium carbonate-urea equilibrium by the necessity of neutralizing acids, either ingested, or formed within the body. The ammonium salts thus formed make up the bulk of the ammonia output in the urine. It is evident, therefore, that the amount of ammonia in the urine depends upon both the extent of urea formation and the amount of acid bodies present in the blood.

In the absence of pathological acidosis, the ammonia output will vary directly with the total nitrogen output. A quantitative increase in the factors of the ammonium carbonate-urea equilibrium results in an increased output of both ammonia and urea. And since protein metabolism leads to the freeing of acid radicles, the ammonia required for the neutralization of these, also contributes to the ammonia excreted. It is noticeable, however, as Folin has shown, that when the body is dependent upon endogenous protein metabolism alone, as a result of a nitrogen-free diet, the ammonia output, while usually reduced, is not diminished proportionately to the diminution in the total nitrogen, of which, therefore, it constitutes a higher percentage. Thus, Folin finds, with a total N-excretion of 16 grams, an ammonia-N output of 0.85 gram (4.3 per cent); while, on a nitrogen-free diet, a total nitrogen output of 3.6 grams was observed with an ammonia-N elimination of 0.51 gram (11.3 per cent). We may assume that this maintenance of the NH_3 output at a proportionately high level is dependent upon a certain constancy in the acid production of the body.

Relations of NH_3 to Acidosis.—The ingestion of mineral acids will, above a certain amount, raise the ammonia elimination. Alkalis will similarly readily diminish that fraction of the ammonia output due to the neutralization of acids, but very large amounts of alkali must be administered further to reduce the ammonia output.

The main clinical interest in the ammonia output is as an index of pathological acidosis. Most organic acids of dietetic or of metabolic origin are changed within the body to carbonates; these carbonates are partly excreted in the urine as such, partly as NH_4CO_3; they also participate in the formation of urea, and partly are dissociated, with liberation of CO_2, which is excreted through the lungs. Mineral acids, however, and many organic acids, especially those of the aromatic series, are normally rendered innocuous by conjugation to form ethereal sulphates, glycuronates, etc., or form neutral salts with the cations of the tissues. Similarly, in pathological conditions of acidosis, of which diabetic acidosis may be taken as the type, the excess acid (in diabetes, β-oxybutyric acid and diacetic acid) must be rendered harmless. To meet this need, ammonia is available and caught up, out of intermediary metabolism, it combines with the acid, thus sparing the fixed cations of the tissues (sodium, potassium, calcium, magnesium). In such conditions, the ammonia output may rise to great heights (8 grams or more a day, in severe diabetic acidosis). In general, any rise in the output above 2 grams a day may be assumed to be due to acidosis.

Relations of NH_3 to Hepatic Function.—There is a possibility, of course, that an increase in the ammonia output to a rather high level might be due to loss of power to form urea. It has been shown that in certain destructive diseases of the liver, the urea output is low, and the

ammonia excretion increased. Coincident acidosis has, however, not been ruled out, and from what is known of urea formation in the tissues, it seems unlikely that deficiency in the urea forming function is at fault. Gross has shown, moreover, that, if ammonium salts be administered in such cases, there is no further increase in the urinary ammonia output noted, and such an increase would seem inevitable if the cause of the high ammonia output were loss of power to form urea.

ii. Quantitative Determination of Ammonia in the Urine

This has a very real practical clinical value in the diagnosis of acidosis. Care in preserving the urine is the first essential for this determination, for ammoniacal decomposition would of course render the results worthless.

Schlösing's method of ammonia determination is time consuming and inaccurate, and will not be described. For clinical purposes, either (1) Folin's method, or (2) the formalin-titration method, will be found most convenient and reliable

1. *Folin's Method*

Principle.—This method is based upon the fact that ammonia is set free from its salts upon the addition of a stronger base (sodium carbonate). The ammonia thus set free is blown over by an air-current into a known amount of N/10-H_2SO_4 solution, and the unneutralized part of the latter determined by titration.

Technic. — Twenty-five c.c. of urine are placed in a graduate 30-40 cm. high, and about 1 gram of anhydrous sodium carbonate and 8-10 grams of sodium chlorid, as well as a little crude petroleum, to hinder foaming, added. The graduate is closed by a doubly perforated rubber cork; through one hole goes a glass tube, which dips into the fluid and serves for the inlet of air; through the other hole passes a glass tube, only about 10 cm. in length. The shorter tube is connected with a "calcium chlorid tube" containing cotton. This, in turn, is attached to a glass tube that reaches to the bottom of a wide-necked half-liter flask

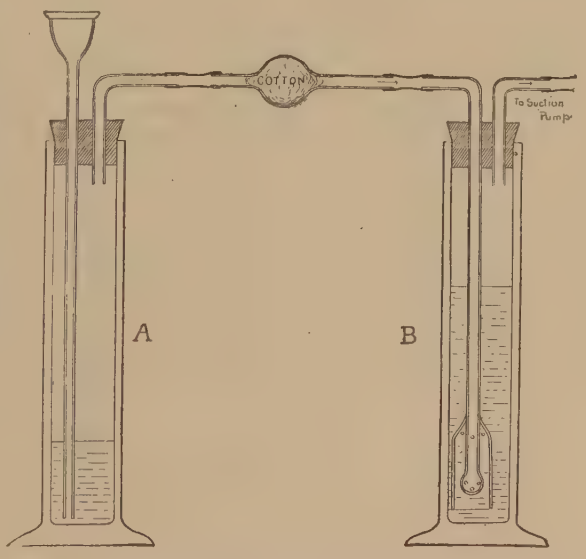

Fig. 434.—Apparatus for the Quantitative Determination of Ammonia According to Folin. Cylinder (A) for Urine, Cylinder (B) for Acid. (After R. S. Morris.)

that contains 20 c.c. of N/10-H_2SO_4 acid and 200 c.c. of water for the absorption of the ammonia. To guarantee complete absorption, the absorption tube in Fig. 434 is used. A good stream of air is blown through, by a water power bellows. A suction pump should not be employed as the results so obtained are unreliable. The ammonia is thus driven from the urine into the absorption vessel in about 1½ hours, at the room temperature.

Two drops of alizarin red (1 per cent aqueous solution) are now added as an indicator to the standard acid solution, which is next titrated with N/10-NaOH, to the first fixed red color. The number of cubic centimeters of tenth-normal acid neutralized by the ammonia is thus easily determined. This number, multiplied by 0.0017 (the NH_3-equivalent of 1 c.c. N/10-acid), gives the ammonia content in grams of the 25 c.c. of urine used. The quantity in the total twenty-four hour specimen is calculated from this.

2. The Formalin Titration Method

Principle.—This method depends upon the fact that the ammonium salts of the urine decompose in the presence of formaldehyd, the acid radicles of these salts being liberated quantitatively as free acid, which is then determined by titration, and the ammonia calculated therefrom.

Technic.—In a 250 c.c. Erlenmeyer flask is placed about 10 c.c. of commercial formalin and 5 drops of 0.5 alcoholic solution of phenolphthalein; N/10-NaOH is added from a buret to the first pale rose color. In a second flask, of similar size, 20 c.c. of urine, 5 drops of the phenolphthalein solution, and 20 grams of finely powdered neutral potassium oxalate, are shaken vigorously together, and then titrated immediately with N/10-NaOH, to the first rose color.

Five cubic centimeters of the neutralized formalin from the first flask are now added to the neutralized urine in the second flask. The pink color disappears, owing to the formation of acid. This acidity is titrated to the first pale rose color with N/10-NaOH. The fixity of this rose color is tested by adding more of the neutralized formalin; if it fades, one titrates further with the N/10-NaOH. The quantity of alkali used to obtain the end-reaction after the formalin has been added represents the number of cubic centimeters of tenth-normal ammonia in 20 c.c. of urine. Each cubic centimeter of tenth-normal ammonia contains 0.0017 gram of ammonia.

Sources of Error.—The error in this method lies in the fact that the amino-acids of the urine are determined by it along with the ammonia. The readings are therefore a little too high. When the excretion of amino-acids is increased, as in diabetes, the error is sufficient to render the method inapplicable to exact metabolic investigations. For ordinary clinical purposes, however, it has proved very satisfactory. It possesses great advantages in its simplicity, and in the rapidity with which a determination can be carried out.

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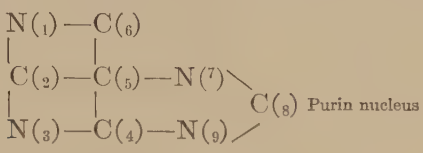
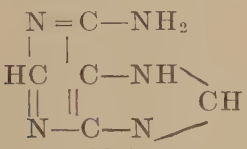
(g) *Purin Bodies in the Urine*

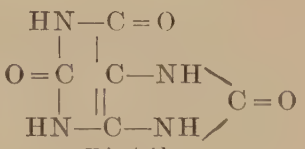
i. Sources of the Purin Bodies of the Urine



The purin bodies are methyl, amino and oxy additives of the purin nucleus and are described by stating to which atom of the purin nucleus the combining groups are attached, *e. g.*

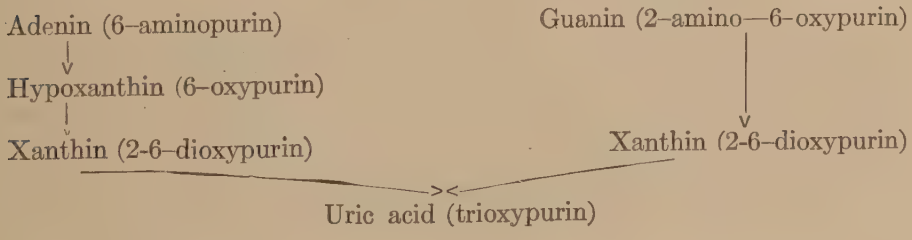


Adenine
(6–Aminopurin)



Uric Acid
(2–6–8–Trioxypurin)

The purins arise as the products of a specialized metabolic process; the metabolism of nucleoproteins. Nucleic acid contains purin groups. The nucleoproteins of the *food* undergo digestive cleavage, the nucleoproteins of the *body* undergo catabolism; and as a result of both processes nuclein is freed from nucleoprotein; nucleic acid from nuclein—and from nucleic acid, phosphoric acid, carbohydrate, pyrimidins and purins are set free. (For details, see Part XIII.) This purin, thus derived from both *exogenous* and *endogenous* sources, now undergoes processes of deamination and of oxidation by which most of the aminopurins are changed to the oxypurins, notably to trioxypurin, uric acid.



The methylpurins (caffein, theobromin) derived from the diet are not converted to uric acid but are excreted as monomethylpurin.

The uric acid in some lower animals is in part oxidized to allantoin by an as yet unknown reaction (uricolysis), due to a ferment uricase; this does not occur in human beings. In man, the uric acid is excreted in the urine together with traces of xanthin, hypoxanthin, monomethylpurins and occasionally still other purin bases.

These traces of purin bases that have not been converted to uric acid and are excreted in the urine, average 16–60 mg. per diem. Xanthin, so excreted, occasionally leads to the formation of calculi. In general, however, the data at present available on the excretion of these bodies other than uric acid have led to no conclusion of clinical value.

ii. The Uric Acid of the Urine

($C_5H_4N_4O_3$, or 2-6-8-trioxypurin)

From the above outline it is plain that the amount of uric acid excreted is influenced by many factors. The determination of uric acid in the urine can be of value only when there is absolute control of the purin intake. Its value is greatly increased by coincident determinations of the uric acid in the blood.

The uric acid excretion averages between .4 and 1 gm. per day. The *endogenous* uric acid excretion varies for different persons, but, in the same person it is very constant. Below .3 gm. constitutes an abnormally low endogenous excretion and above .6 gm. an abnormally high one (Brugsch). The *exogenous* uric acid excretion, which varies in amount with the character of the food, may bring the total excretion of uric acid as high as 2 grams. Only about 1–2 per cent of the total nitrogen of the urine comes from uric acid.

Conditions in which there is excessive destruction of body cells (leukemia; absorption of pneumonic exudates; after x-ray exposures) lead to an increase in the excretion of uric acid. Active muscular exercise also increases it, owing partly to metabolism of inosine of muscle.

The ability of the kidney to excrete uric acid is limited, and the conditions of excretion are not yet well understood; in renal disease there is often retention of uric acid.

The complex relationships of the purin metabolism to gout are discussed under that disease. The uric acid excretion in the urine is not of as much clinical value in the study of gout as is the determination of the uric acid in the blood. In chronic gout the output of uric acid in the urine in the intervals between attacks is diminished while the uric acid content of the blood is increased (uricemia); during an attack uric acid may be excreted in larger amounts than normal. The excretion of

exogenous purins normally occurs within 48 hours after ingestion; in gout, this elimination is often markedly delayed, and this delay seems to be related to the severity of the disease.

Uric acid is a dibasic acid forming two series of salts (urates); *e. g.*, disodium urate and monosodium urate (or acid urate). A so-called hemisodium urate, in which two molecules of uric acid are combined with one atom of sodium, also occurs.

The uric acid of the urine is partly dissolved as such (chiefly in so-called supersaturated solution), partly in the form of its salts (monosodium urate; hemisodium urate). The *brick dust deposit* or *lateritious deposit* that falls out of a concentrated urine on cooling consists of amorphous hemisodium urate. It re-dissolves on heating, or on addition of NaOH.

Free uric acid is scarcely at all soluble in water; in hyperacid urines, it may fall out in the form of a heavy bright yellow, or yellowish red, crystalline sediment, which, under the microscope, is found to consist of whetstone-shaped, comb-shaped, barrel-shaped, or spear-shaped *crystals of uric acid.* Occasionally, such crystals of free uric acid are precipitated in the pelvis of the kidney, or in the bladder, and can be the starting point of calculi, or of hemorrhages. In ammoniacal urine, thorn-apple *crystals of monoammonium urate* are often seen.

iii. Qualitative Test for Uric Acid, or Urates (Murexid Test)

This may be applied to urinary sediments, needlings of gouty tophi, urinary calculi, the blood in gout, etc. A few of the crystals, or a little of the mass to be examined, are placed upon a porcelain dish and a few drops of nitric acid added. One may heat briskly at first, but toward the end must avoid strong heating and evaporate slowly to complete dryness over the water bath, blowing constantly. At first, a yellowish color appears which, on complete drying, assumes a red tinge. If now a drop of ammonia be added with a glass rod, or if the evaporating dish be simply exposed to ammonia fumes, a beautiful purple red color appears; (or if a drop of NaOH instead of ammonia be used a bluish violet color is seen). Excess of ammonia or of NaOH is to be avoided.

iv. Quantitative Determination of Uric Acid

1. The Hopkins-Folin-Shaffer Method

Principle.—This method depends upon use of the fact that ammonium urate is insoluble in concentrated solutions of other ammonium salts, and hence uric acid and its salts may be precipitated quantitatively as ammonium urate. Sulphuric acid is added to the ammonium urate, thus liberating uric acid. Uric acid in a sulphuric acid solution reduces and thereby decolorizes weak solutions of potassium permanganate. The

amount of uric acid is therefore determined by titrating with N/20-K_2MnO_4.

Solutions Required.—These include: 1. 500 grams of ammonium sulphate and 5 grams of uranium acetate dissolved in 650 c.c. water and 60 c.c. 10 per cent acetic acid added; the volume of the solution is then brought to 1 liter.

2. A 10 per cent solution of ammonium sulphate.

3. N/20-$KMnO_4$ solution. (1.581 gm. pure K_2MnO_4 in 1 liter of water. Standardize against N/20-oxalic acid.)

Technic.—300 c.c. of urine are mixed with 75 c.c. of the above solution containing uranium acetate, stirred thoroughly, and allowed to stand for five minutes to give the precipitate time to form; the fluid is then filtered through two folded filters, and in each of the two beakers 125 c.c. of the filtrate (corresponding to 100 c.c. of urine) are placed. The uranium acetate precipitates phosphates and other substances that might interfere with the accuracy of the test. To each beaker is then added 5 c.c. of strong ammonia. After thorough stirring, the mixture is set aside until the following day. Ammonium urate will be found as a sediment at the bottom of the beaker. The supernatant fluid is carefully poured on a small smooth filter, and, finally, the precipitate itself is washed upon the filter by means of the 10 per cent solution of ammonium sulphate, until the filtrate no longer yields a positive qualitative reaction for chlorids. The residue is washed several times. The precipitate is now washed into a beaker, using about 100 c.c. of water. It is best in doing this to take the filter out of the funnel and to open it instead of poking a glass rod through it. To the ammonium urate suspended in about 100 c.c. of water, 15 c.c. of concentrated H_2SO_4 are now added, and the solution, while still warm, titrated with N/20-$KMnO_4$ solution. Toward the end of the titration it is well to add the permanganate solution two drops at a time until the first feeble rose color permeating the whole fluid becomes visible and persists for 30 seconds. Each cubic centimeter of N/20-$KMnO_4$ solution corresponds to 3.75 milligrams of uric acid. On account of the solubility of ammonium urate the results are corrected by adding 3 mg. of uric acid for each 100 c.c. of urine.

2. Folin and Denis's Colorimetric Method

Reagents.—1. The Uric Acid Reagent.—This solution contains 10 per cent of sodium tungstate and 16 per cent of phosphoric acid boiled together for about two hours. To 750 grams of water add 100 grams of the tungstate and 80 c.c. of 85 per cent phosphoric acid (H_3PO_4). Boil gently for two hours using a reflux condenser to prevent undue concentration, cool and dilute to 1 liter. Two cubic centimeters of this solution give the maximum color obtainable with 1 mg. of uric acid.

2. The Standard Uric Acid Solution.—One gram of uric acid in a volumetric liter flask is dissolved by means of an excess of lithium carbonate (200 c.c. of a 0.4 per cent solution). To the solution are added 40 c.c. of 40 per cent formaldehyd solution and the mixture is shaken and allowed to stand for a few minutes. The clear solution is acidified by the addition of 20 c.c. of normal acetic acid and the

whole is diluted up to the liter mark with water. The solution should remain perfectly clear and the next day (but not before) it can be standardized against a freshly prepared lithium carbonate solution of uric acid. The color produced by 5 c.c. of the solution corresponds very nearly to the color obtained from 1 mg. of uric acid. The colorimeter reading obtained for the solution when thus compared against 1 mgm. of pure uric acid is, of course, thereafter to be used as the standard value corresponding to 1 mg. of uric acid. The solution obtained in this manner seems to keep its strength indefinitely.

Technic.—From 1 to 2 c.c. of urine are measured into an ordinary centrifuge tube by means of a modified Ostwald pipet. A sufficient amount of distilled water is then added to bring the volume of the liquid in the tube to about 5 c.c. Six drops of 3 per cent silver lactate solution, two drops of magnesia mixture, and a sufficient amount (10-20 drops) of concentrated ammonium hydrate to dissolve the silver chlorid are then added. The tube is now centrifuged for one or two minutes, the supernatant liquid poured off, and to the residue in the bottom of the tube are added five or six drops of freshly prepared saturated hydrogen sulphid water and one drop of concentrated hydrochloric acid, and the tube is placed in a beaker of boiling water until all excess of hydrogen sulphid has been driven off.

As hydrogen sulphid gives a blue color with the "uric acid reagent" care must be taken to obtain its complete removal. To determine whether this has been accomplished one drop of 0.5 per cent lead acetate solution should be added to the contents of the tube after the latter has remained in the water bath for about five minutes and if any hydrogen sulphid still remains a dark brown precipitate will be formed. If this condition be obtained, the tube should be returned to the water bath for a further period of heating.

When the tube has been cooled, add 2 c.c. of the uric acid reagent, and 10 c.c. of saturated sodium carbonate solution. Transfer to a 50 c.c. volumetric flask and make up to volume. The color comparison is then made in the usual manner in a colorimeter against the color obtained from 5 c.c. of the standardized uric acid formaldehyd solution (or a freshly prepared pure uric acid solution).

In the case of urines containing much albumin, it will be found that after the addition of hydrogen sulphid the solution obtained is invariably of a brownish tint, which interferes with the color comparison, and thus makes accurate readings very difficult. This difficulty may be overcome by adding to the hot solution (after the removal of all hydrogen sulphid) from two to ten drops of a 10 per cent sodium acetate solution.

This procedure has also been found useful in the determination of uric acid in blood where the same trouble is met with when, as occasionally happens, the protein has not been entirely removed.

Unless albumin be present, sodium acetate should not be added either in blood or urine analysis, as its presence tends to give slightly low results.

v. Quantitative Determination of Uric Acid and of Purin Bases (Method of Rudisch and Kleeberg)

This method makes it possible to determine both the uric acid and the purin bases. All the purin bodies of the urine are precipitated with excess of a standard $AgNO_3$ solution. The uncombined silver is determined by titration with standard potassium iodid solution, using a mixture of nitrous and sulphuric acid with starch solution as an indicator. If uric acid alone is to be determined, the purin bases may be redissolved by addition of ammonia before titration. For details, see the original publication.

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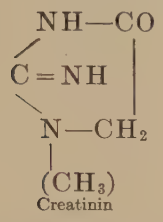
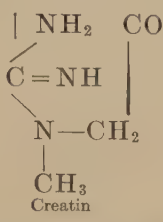
(*h*) *Creatinin and Creatin*



Creatinin



Creatin

Creatinin is a normal constituent of the urine, being excreted daily in amounts varying between 1 and 2 grams.

i. Sources of Creatinin

The sources of creatinin are exogenous and endogenous. *Exogenous creatinin* is derived from the preformed creatinin in meat. This creatinin is in part changed to urea in the body, and in part excreted as creatinin. *Endogenous creatinin* can be best studied when the patient is on a meat free diet; the protein intake has then no effect upon the creatinin output, the latter being wholly derived from the muscular metabolism; it does not represent a stage in the metabolism of foodstuffs. Under these conditions, the creatinin-nitrogen output is quite independent of the total nitrogen. Accordingly, when the total nitrogen output is much diminished, the creatinin percentage is high. On a nitrogen free diet, creatinin constitutes about 18 per cent of the total nitrogen.

The formation of endogenous creatinin is not well understood, though the output is, for each person, a constant related to the mass of muscular tissue.

It is probable that creatinin arises directly from creatin, of which it is the anhydrid. Creatin is found in the muscle plasma; on anhydration, the creatinin formed is excreted in part as such, and in part is changed to urea. But the origin of creatin is not clear; it is assumed that amino-acids are the source.

In certain conditions, creatin appears in the urine, owing probably to failure to convert creatin into creatinin in intermediary metabolism, analogous to the failure to burn β-oxybutyric acid in diabetic acidosis. Failure to transform creatin (and its consequent excretion) occurs physiologically in children and in women during menstruation, pregnancy and lactation; in men, however, creatin is not found in the urine except under pathological conditions (Krause); namely

(1) in general wasting, as in cancerous cachexia; (2) in rapid degeneration of muscle tissue, as in neuritis and myelitis; (3) in diabetes mellitus and in phloridzin diabetes.

The excretion of creatin in diabetes seems to be connected with the failure in carbohydrate metabolism in the same fashion as the excretion of ketone bodies. In the absence of glucose combustion, creatin is not transformed to creatinin, just as β-oxybutyric acid is not oxidized completely. Future investigations must determine in how far this relationship determines all cases of creatin excretion.

The significance of the variations in creatinin excretion, in the absence of creatin in the urine, is also largely a question for the future to decide. On account of its purely endogenous derivation (on a meat free diet), and its constancy in a given person, creatinin has been assumed by some to be an index to the sum of all endogenous metabolism. That this is not so is made evident by its independence of conditions of increased catabolism in tissues other than muscle. It can be looked upon only as a measure of a special metabolic process in muscle cells. Its production bears no direct relation, however, to the function of contractility. Normal muscular movements cause no increase in creatinin excretion (Taylor). Creatinin is formed in constant quantities in muscle tissue, as a part of the life of the muscle cell.

The behavior of this special metabolic process under conditions of disease is yet very incompletely known.

ii. Qualitative Test for Creatinin (Jaffé)

Technic.—Five cubic centimeters of urine are boiled to drive off any acetone present. On cooling, a few drops of a saturated solution of picric acid and a few drops of dilute sodium hydrate solution are added. In the presence of creatinin an intense red color appears, which changes to yellow on addition of acetic acid.

iii. Quantitative Determination of Creatinin and Creatin (Folin)

This method is based upon a comparison of the color produced by Jaffé's test with that of a standard solution of permanganate. A high grade colorimeter is necessary.

Creatin is changed into creatinin by heating the urine, to which phosphoric acid has been added, to 120° C. for 30 minutes. The amount of creatinin in untreated urine is subtracted from the total creatinin (determined after conversion of the creatin) to obtain the amount of creatin present. For the details of the method, Folin's paper should be consulted.

The use of creatinin in functional renal diagnosis is described in Part X.

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(*j*) *Undetermined Nitrogen of the Urine*

The nitrogen of the bodies constituting this group amounts to 4–7 per cent of the total N. The substances in this group are not associated by any common significance in a physiological sense further than that they are practically all derived directly or indirectly from protein substances of the food or tissues. For convenience in discussion the more important of these bodies from the point of view of the clinician are taken up under the following headings:

1. The aromatic compounds in the urine.
2. The nitrogenous bodies containing "neutral sulphur."
3. The amino-acids, the amins and the diamins.
4. The urinary pigments.
5. Mucin bodies.

The discussion of the last three of these headings is postponed. Their association with certain pathological constituents is such that it is best to take them up in that connection.

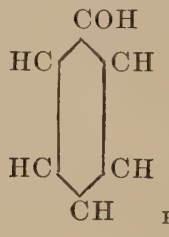
i. Aromatic Compounds in the Urine

Aromatic compounds in the urine are derived almost entirely from resorption of the aromatic bodies in the intestinal contents. Metabolic processes in body tissues free aromatic compounds (aromatic amino-acids), but these are not excreted in the urine. The benzene ring is ruptured and the product oxidized. The aromatic bodies resorbed from the intestines apparently cannot be so treated.

The aromatic bodies in the intestinal contents are made up of (1) the aromatic amino-acids (phenylalanin, tyrosin, tryptophan), arising from the protein of the food, (2) derivatives of these amino-acids due to bacterial putrefaction, (3) aromatic bodies in fruits, vegetables, (4) derivatives of these, due to digestive hydrolysis or to bacterial action.

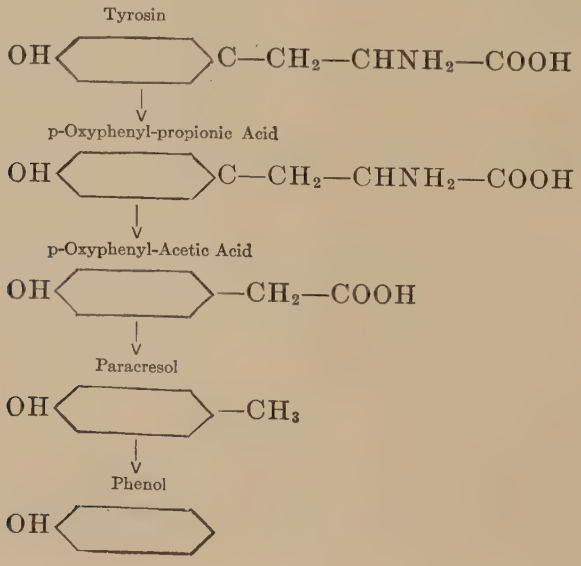
The resorption of the aromatic amino-acids is followed by their entrance into the endogenous protein metabolism. The resorption of the other aromatic bodies of the intestinal contents is followed in part by their combustion, and in part by their conjugation with sulphuric acid (forming ethereal sulphates), with glycuronic acid (forming glycuronates), or with glycocoll (paired amino-acid), and by their subsequent excretion in the urine. In other words, these aromatic bodies apparently cannot be burned completely, and must be rendered harmless and excreted. Aromatic substances, appearing in the urine as a result of this protective process in the body, may be grouped roughly under three headings: the phenol group; the indol group; and hippuric acid.

1. *The Phenol Group*



Phenol

From the aromatic amino-acids, tyrosin and phenylalanin, by bacterial oxidative and reductive processes, a series of aromatic substances is derived, the end-product of which is chiefly phenol.



Phenol is likewise derived from certain aromatic bodies present in fruits and vegetables. It may also be ingested medicinally or with suicidal intent.

Of the phenol in the intestines, derived from these sources, a part is oxidized further to hydrochinon and a part to orthodioxybenzene, while what then remains is absorbed. There is also some absorption of the intermediary bodies in the formation of phenols and of the bodies derived from the oxidation of phenol.

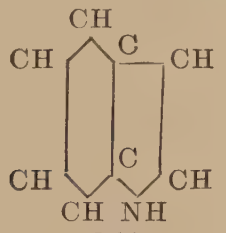
After resorption, some of the phenol undergoes combustion in the body. A greater part is conjugated with sulphuric acid derived from the catabolism of cystin.

$$C_6H_5OH+HO.SO_3K=C_6H_5O\ SO_3K+H_2O$$

This conjugation takes place in the liver. When the amount of phenol is large (poisonings), conjugation also occurs with d-glycuronic acid (derived from the metabolism of glucose). The ethereal sulphates thus formed, while distinctly toxic, are much less so than phenol itself (Metchnikoff).

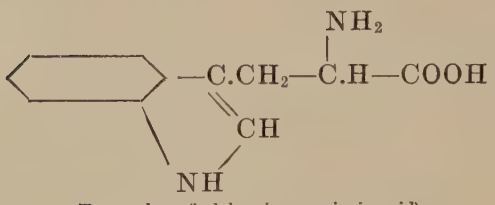
In the urine, phenol appears normally in small quantities, from 0.005 to 0.07 gram a day. A trace of this phenol is in the free form; the greater part is conjugated with sulphuric acid. Likewise traces of intermediary bodies in the formation of phenol from tyrosin, and traces of bodies derived by oxidation from phenol, appear in the urine either as simple salts, or, in other cases, conjugated with sulphuric acid. Such are paracresol, para-oxyphenyl-acetic acid, para-oxyphenyl-propionic acid, hydrochinon, etc.

2. *The Indol Group*

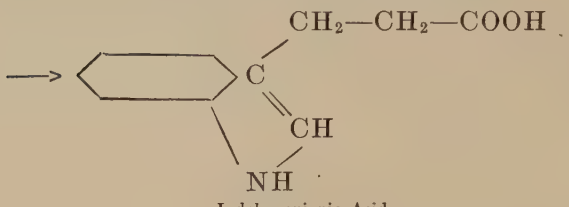


Indol

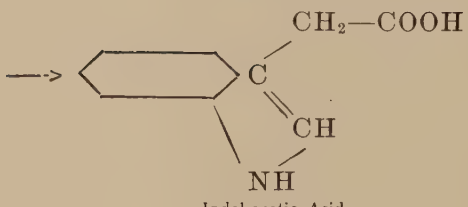
Whereas phenol arises from several sources, indol and its derivatives are derived from bacterial putrefaction of a single amino-acid, tryptophan. The tryptophan in the intestinal contents comes from digestive cleavage of the protein of the diet and of the protein in the gastro-intestinal mucin. By bacterial action tryptophan gives rise to numerous bodies.



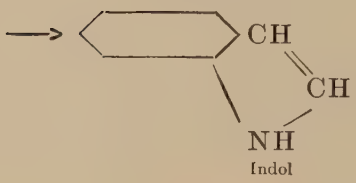
Tryptophan (indol-amino-propionic acid)



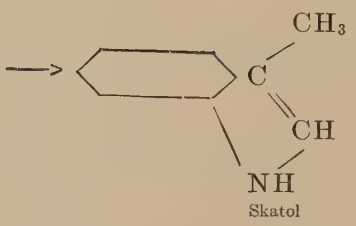
Indol-propionic Acid



Indol-acetic Acid

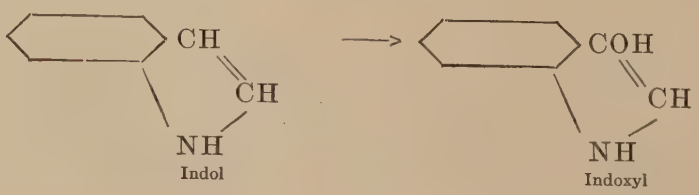


Indol



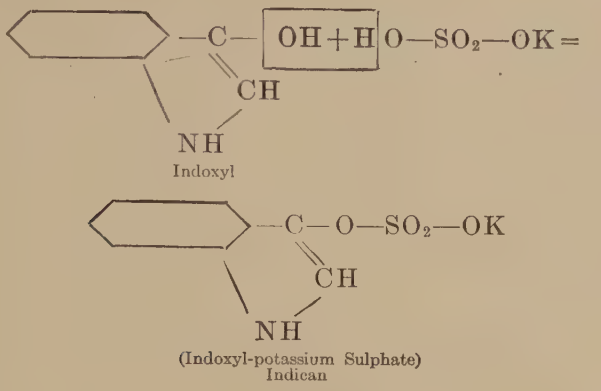
Skatol

The indol and skatol thus formed in the intestine are resorbed and undergo oxidation in the body.



Indol Indoxyl

The indoxyl and skatoxyl are then conjugated in the liver with sulphuric acid.



The indican thus formed is excreted in the urine. Skatoxyl, conjugated with sulphuric acid, is also excreted in minute quantities. Indolacetic acid has been found in the urine and shown to be the chromogen of the pigment *urorosein.*

The average daily excretion of indican, as determined by Wang's method, ranges between 5 and 20 mg. On a diet that is nitrogen free, or in which the protein present contains very little tryptophan (milk, eggs, gelatin, arrowroot), the reaction for indican disappears from the urine. In cases of intestinal obstruction, of ileus, of peritonitis, and occasionally in simple constipation, the amount is distinctly increased. Jaffé has shown that in obstruction of the large intestine there is no increased indicanuria until stasis of the ileum also occurs. This is probably a question of resorption being greater from the small intestine. It is stated that in cases of putrid decomposition of protein elsewhere in the body than in the intestine, as in gangrene, putrid bronchitis, ulcerating cancers, etc., the amount of indican in the urine is increased. The significance of these facts will be discussed later.

Urine containing large amounts of indican may, upon standing, develop a bluish scum. This is due to the oxidation of indican to indigo. In some cases this process occurs in the body, and the urine on voiding has a bluish color.

Qualitative Test for Indican (Obermayer's Test)

To a few c.c. of urine add an equal amount of Obermayer's reagent (conc. HCl containing 0.2 per cent ferric chlorid). Mix well. Two c.c. of chloroform are then added, and the tube inverted several times. The indigo formed dissolves in the chloroform. On standing the chloroform quickly separates, and if indican be present, will show a blue or purplish violet color. Iodids or salicylates give a red violet or a rose color, which may mask a weak indican test.

Quantitative Determination of Indican (Wang's Method)

This method consists in the oxidation of indican to indigo, and the change of indigo to indigosulphuric acid, which is then titrated with potassium permanganate solution. The oxidation of the indigosulphuric acid renders it colorless or pale yellow.

This method is probably the most accurate of those devised, but it is not suitable for clinical use (see larger texts).

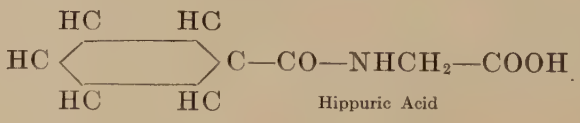
Quantitative Determination of Indican (Folin's Method)

This method is simple, but it is only roughly accurate, and the results obtained are in terms of an arbitrary scale adopted for convenience. The color of the urine, when treated with Obermayer's reagent, is compared with the color of Fehling's solution, as a standard, to which the arbitrary value 100 has been given.

One one-hundredth of the total 24 hour urine is mixed with an equal volume of Obermayer's reagent (*vide supra*). The mixture is then thoroughly extracted with 5 c.c. of chloroform until all of the indigo has been dissolved. The chloroform solution, colored with indigo, is then compared colorimetrically (Duboscq colorimeter) with the color of Fehling's solution. On a diet of 119 grams of protein, Folin found the average indican excretion to be 77. On a nitrogen free diet no indican is found.

The colorimetric method of Autenrieth and Funk (*vide* reference) may also be employed.

3. *Hippuric Acid*



Hippuric Acid

Hippuric acid is formed as a result of the synthesis of benzoic acid with the amino-acid glycocoll.

$$\underset{\text{Benzoic Acid}}{C_6H_5—COOH} + \underset{\text{Glycocoll}}{H_2N—CH_2—COOH} \longrightarrow \underset{\text{Hippuric Acid}}{C_6H_5.CO—N.H—CH_2—COOH} + \underset{\text{Water}}{H_2O}$$

The benzoic acid that is eliminated in this form is derived by resorption from the intestines, where it occurs in the fruit and in the vegetables of the diet, or is formed from other aromatic bodies in the fruits and vegetables, by digestive cleavage, or by bacterial action. It is probable that the aromatic amino-acid phenylalanin, whose decomposition results chiefly in phenol, may also be the source of a certain amount of benzoic acid.

Many aromatic compounds exist, such as toluol, nitrobenzoic acid, phenyl b-lactic acid, etc., which, when ingested, are oxidized in the animal body to benzoic acid.

The benzoic acid, thus derived, is resorbed, and in the body is conjugated with glycocoll. Glycocoll takes a part alike in the anabolism and in the catabolism of protein, and is, therefore, constantly present. If,

however, the quantity in which it is present be insufficient, there is evidence that the body catabolizes protein to furnish the necessary glycocoll.

The chief site of the synthesis of hippuric acid is probably in the kidney. It is a ferment action. It has been stated that in certain nephropathies this function is impaired.

On a mixed diet the excretion of hippuric acid varies from 0.3-1.0 gm. a day; on a fruit and vegetable diet it may rise to 2 gm. or over. Prunes, cranberries, bilberries and green gages contain large amounts of benzoic acid.

4. Significance of the Aromatic Bodies in the Urine

A conservative interpretation must be made of the excretion of the aromatic bodies. Their sources, their resorption and their metabolism are all too variable and too little known to allow of rigid definition.

Measurement of the ethereal sulphates is often taken as a means of estimating the excretion of phenol and indol bodies, and from the amount of ethereal sulphates the extent of the putrefactive processes in the intestines is inferred. There are serious objections to this assumption. In the first place, the ethereal sulphates are not entirely made up of conjugated phenols and indols, and hence may vary independently of these bodies. All phenols and indols absorbed from the intestines are not conjugated with sulphuric acid. Unknown amounts are burned, and some are conjugated with glycuronic acid. The amount of phenols and indols absorbed is not definitely proportionate to the amount formed in the intestines.

In the same way, there are good reasons for refusing to attach any significance to the appearance of a qualitative test for indican in the urine. The most that this occurrence justifies us in saying is that some indol has been resorbed from the intestine as a result of the putrefaction of tryptophan. But it does not enable us to state that the putrefactive process is any more intense than normal. Somewhat greater significance, of course, attaches to the demonstration by quantitative methods of a large and persistent increase in the indican excretion above normal figures. Indoxyl itself is considered by some as a toxic body. The data as to the toxicity of conjugated indoxyl are at present very incomplete.

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ii. Nitrogenous Bodies of the Urine Containing Neutral Sulphur

These include sulphocyanates, taurocarbamic acid, cystein, chondroitin-sulphuric acid, uroferric acid, oxyproteic acids.

These substances, of various origins, and significance, are here grouped together as nitrogenous bodies, characterized by their content of organically bound sulphur (so-called neutral sulphur). The significance of the group in the metabolism of sulphur will be discussed under that head. The significance of the single members of the group will be briefly alluded to here.

Sulphocyanates.—The *sulphocyanates,* which are found in minute quantities in normal urine, are probably derived by resorption of sulphocyanates in swallowed sputum.

Taurocarbamic Acid.—This is likewise present in traces, and is probably derived from the biliary secretions.

Cystein and Cystin.—A trace of one or both of these substances may be found in normal urine (*vide* Cystinuria).

Chondroitin-sulphuric Acid.—Traces of this body, which is a constant constituent of cartilage, are found in normal urine (Mörner). The relations of this acid to amyloid are of interest.

Uroferric Acid.—A decomposition product of the oxyproteic acids (Bondzynski).

Oxyproteic Acids.—These acids (alloxyproteic acid, antoxyproteic acid, oxyproteic acid, etc.) are sulphur-containing, nitrogenous bodies apparently of polypeptidlike nature. A great deal of their nitrogen is in the amino form. Various amino acids have been recovered in their analysis; among them cystin, and arginin (Glagolew), which probably account for the sulphur content. In normal cases, the nitrogen excreted in this form constitutes from 3 to 5 per cent of the total nitrogen. It is apparently increased by a meat diet.

The significance of this fraction of the total nitrogen is not yet clear. It seems evident that the oxyproteic acids are intermediary bodies in the catabolism of proteins. It is possible that they are further catabolized in the body, and that their excretion is simply a consequence of their presence in the blood at one stage of this process. It is also possible that they are produced in the catabolism of some type of tissue-protein as end-bodies that are resistant to further cleavage.

Colloidal Nitrogen.—Upon the addition of absolute alcohol to albumen-free, concentrated, urine, a precipitation of some of the bodies present in colloidal solution occurs. The nitrogenous content of this precipitate has been given the name of "colloidal nitrogen." [Salts of heavy metals, Hg., Pb., etc., have been used by some in place of absolute alcohol.] This colloidal nitrogen is derived from precipitated oxyproteic acids, and N-containing carbohydrates (dextrins) (Salkowski). Normally it constitutes 3–6 per cent of the total N; in cases of carcinoma, however, it is often increased to 9 per cent of the total nitrogen. This fact has been thought to be due to something specific in cancer metabolism and hence to be of diagnostic value. The blood of carcinoma cases has been shown to contain specific ferments capable of breaking down carcinoma protein *in vitro*. (Dick.)

But further investigation has shown that similar, though less marked, changes in the colloidal N percentage are found in phthisis, diabetes, pernicious anemia, etc.; and at present it is held that, although marked increase in the colloidal nitrogen fraction indicates the occurrence of abnormal catabolism of protein, the evidence does not at present justify assuming any marked specificity in this process.

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3. The Non-nitrogenous Organic Constituents of the Urine

The urine normally contains few of the products of the metabolism of fat and carbohydrates; its organic constituents are, as we have seen, chiefly

nitrogenous bodies, the results of protein metabolism. It is probable that even the non-nitrogenous organic constituents are derived from protein.

(*a*) *Volatile Fatty Acids*

In the normal urine are found traces of volatile fatty acids whose source is unknown. They are held to arise from bacterial action upon carbohydrates in the intestine, but more recent work points to the decomposition of amino-acids as their source (Neuberg and Rosenberg). They would, therefore, seem to be of similar significance to the indol and phenol bodies in the urine. Their amount is increased (*lipaciduria*) in cases of decomposition of protein material (*e. g.*, purulent collections) within the body. For methods, see larger handbooks.

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(*b*) *Oxalic Acid* $\begin{matrix}\text{CO.OH}\\ |\\ \text{CO.OH}\end{matrix}$

In the normal urine oxalic acid is found in daily amounts of 10-20 mg. Exogenous oxalic acid is preformed in the diet. Certain vegetables—carrots, spinach, rhubarb, tomatoes, etc.—contain relatively large amounts of this substance. But even if a patient be placed upon an oxalate free diet, the urine will still contain traces of oxalic acid. The source of this endogenously formed acid is not yet determined. Attempts to connect it with the purin or with the creatinin metabolism have yielded no conclusive results.

Oxalic acid is increased in cases of jaundice and in certain cases of pulmonary phthisis. But the so-called oxaluria, the diagnosis of which was based upon the presence of certain neurasthenic symptoms in association with calcium oxalate crystals in the urine, is not a clinical entity.

The presence of calcium oxalate crystals in the urine is practically independent of the amount of oxalate excreted. In terms of the solubility of calcium oxalate in water every urine is a supersaturated solution; but the urine contains protective colloids, which enable it to hold in solution far greater quantities of salts than can be dissolved in similar amounts of pure water. Changes of state in the colloids of the urine probably play an important part in the precipitation of the calcium oxalate crystals. The reaction of the urine appears to be of very slight significance. These

facts are important in view of the occurrence of oxalate stones in the genito-urinary tract. Calcium oxalate crystals themselves have long been known to be associated with dysuria and even hematuria (Roberts), due to their irritative action on the mucosa of the urinary passages.

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4. The Inorganic Constituents of the Urine

For the general significance of mineral matter in metabolism, see Part XIII. Here we shall take up the special significance of the single mineral substances of the urine and the methods of investigating them.

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I. THE INORGANIC ANIONS

(a) *Chlorids (Cl)*

i. Sources, Distribution and Excretion of Chlorids

The average amount of chlorids (calculated as NaCl) excreted in the urine is 10-15 grams a day. Both inorganic chlorids and chlorids in organic combination occur in the *diet*. Of the inorganic forms, potassium and calcium chlorids are present chiefly as primary constituents of the food, while the sodium chlorid intake is largely due to the addition of this salt as seasoning. Chlorids in organic combination are found in vegetable foods (Köppe).

In health, *resorption* of sodium chlorid from the intestines is almost complete, only a trace appearing in the stools. Very little work, however,

has been done that throws any light upon resorption of chlorids in disease. There is some evidence that it may be markedly disturbed. In certain cases of cardiac decompensation chlorids administered orally are not excreted in the urine within the normal period; nevertheless, the patients show normal excretion of intravenously administered chlorids —a phenomenon that has been explained as due to a failure of resorption of the ingested salt. Bauer also has noted, in infants suffering with intestinal disturbances, a large excretion of chlorids in the stools. A word may be said regarding the *distribution* of chlorids in the body. Chlorids in various proportions are present in all the tissues. The body fluids—blood, lymph and pathological transudates and exudates—contain the greater part of the chlorids. In the analyses of the organs chlorids are most abundant in the skin, the intestines, the liver and the lungs, in the order named. How much of the chlorid of the body is in the form of free inorganic salts and how much in various combinations with the colloidal substances of the body fluids and tissues is not known.

The *excretion* of chlorids is chiefly through the kidneys. In the stools normally only a trace is found, though it is possible that in diseased conditions a considerable proportion of the chlorid excretion may follow this route. The average chlorid excretion in the sweat is given by Gautier as 1.2 grams. From what is known of the very wide variations in the amount of sweat (0.3-6.0 liters), it is apparent that the excretion of chlorids by this path demands consideration in any investigation of chlorid balance. The excretion of hydrochloric acid in the gastric juice is probably followed by a reabsorption of the chlorids thus excreted; and the same holds true for the chlorids in the saliva.

ii. The Cl Balance of the Body

The *normal body* maintains an equilibrium in chlorid intake and output. Ingestion of larger amounts of salt than usual may be followed by a temporary retention, but the elimination is usually very prompt as contrasted with that of certain other mineral bodies (*e. g.*, calcium lactate). Quite characteristic for chlorids is likewise the cessation of excretion under conditions of starvation. Chlorids in the urine are reduced to a mere trace; the body will not reduce its chlorid content beyond a certain point. Chlorid balance can, therefore, be maintained on an exceedingly small chlorid intake; but the optimal chlorid intake of the normal person is probably higher than this minimal amount.

The rôle of the chlorids in the general metabolism of the body is less specifically known than that of the phosphates and sulphates. Its properties as an anion of freely dissociated salts—that is, its non-specific properties—are probably of the greatest importance in the maintenance of various physicochemical equilibria in the body fluids and tissue cells.

The chlorids may be displaced to a certain extent in the body by the bromids. The administration of bromids to a patient does not result in any increase in the body content in halogens, but leads to a diminution in its chlorid content due to the substitution of bromids.

According to Bunge, sodium chlorid has a specific rôle to play in freeing the blood of the excess potassium phosphate derived from the vegetable constituents of the diet. The interaction of these salts yields potassium chlorid and sodium phosphate, which are readily excreted in the urine. In view of this theory, the preponderance of potassium over sodium salts in a mixed diet furnishes a reason for the custom of adding salt to food.

Pathological disturbances of chlorid equilibrium have been studied chiefly in relation to **edema,** to nephritis and to febrile disease. Certain facts as to the behavior of the chlorid excretion in the urine in these conditions have been established. But accurate knowledge as to the chlorid balance can hardly be said to be available, and the whole question as to the rôle of the chlorids in edema is in the utmost confusion.

In brief, it is known that in certain cases of edema, especially in those related to myocardial insufficiency or to nephritis, ingested sodium chlorid is not excreted in the urine within the normal period, and it is assumed that it is partly retained in the tissues. A retention of water may occur simultaneously. Moreover, during the diuresis that accompanies the disappearance of these forms of edema, the chlorid output in the urine is in considerable excess of the chlorid intake. The occurrence of such a retention of chlorids running a course parallel to that of the edema is indisputable, though it is not a constant phenomenon.

Loeb and others have related edema to an increase of osmotic pressure in the tissues, due to the accumulation of crystalloids. This increased osmotic pressure leads to inflow of water from the circulating fluids, and, as a consequence, to edema of the tissues. In the terms of this theory the chlorids retained in specific tissues (historetention), by their influence on the osmotic pressure are productive of edema (Strauss). For a further discussion of seroretention and historetention of Cl, see Functional Renal Diagnosis (Part X).

Fischer, however, considers that edema is due to increased hydration capacity of the tissue colloids. This increase in the capacity of colloids to take up water occurs in the presence of acids such as are formed in the tissues during metabolism, and, according to Fischer, salts diminish this affinity of the hydrophilic colloids for water. Sodium chlorid, then, far from being causative of edema, would play a part in its prevention!

Clinically the deficiency of the kidney in certain nephropathies, in its function of excreting salt, has been made use of as a functional test. (*Vide* Section X).

It has been long known that in febrile conditions, and notably in pneumonia, there occurred a marked *retention of chlorids,* followed later

by a compensatory increased excretion. The attempts to make use of this fact in diagnosis and prognosis have, however, proven fruitless.

iii. Quantitative Determination of the Chlorids of the Urine

Such determinations are frequently necessary in the study of renal function and of other conditions.

1. *The Lüttke-Martius Modification of the Volhard Method*

Principle.—This method is based upon the precipitation of chlorids by silver nitrate and the titration of the excess of silver nitrate by ammonium thiocyanate using iron-ammonium-alum as an indicator. It is not necessary to remove albumin, if any is present.

Technic.—Two standardized tenth-normal solutions are required:

1. The silver nitrate solution contains:
   (a) 17.5 gm. $AgNO_3$.
   (b) 900 c.c. HNO_3 (25 per cent).
   (c) 50 c.c. of a cold saturated solution of iron-ammonium-alum.
   (d) Distilled H_2O to 1,000 c.c.

This solution should be standardized by titration against N/10-HCl, using ammonium thiocyanate as an indicator. Dilution, if necessary, is done by addition of a solution made up of 25 per cent conc. HNO_3, 5 per cent sat. iron-ammonium-alum, and 70 per cent distilled H_2O. The standardized solution keeps well in a brown bottle, away from the light.

2. The ammonium thiocyanate solution contains:
   (a) 8.0 gm. NH_4SCN.
   (b) 1,000 c.c. distilled H_2O.

The solution is then standardized by titration against the N/10-$AgNO_3$ (solution No. 1).

Ten c.c. of urine are pipetted into a 100 c.c. volumetric flask; 20 c.c. of N/10-$AgNO_3$ are added; the mixture is gently agitated and then allowed to stand for five minutes to ensure complete precipitation of the chlorids. Distilled water is then run in up to the 100 c.c. mark. The flask is shaken. If the mixture has a reddish tinge a few drops of a solution of potassium permanganate are added to clear it. The precipitate of silver chlorid is now removed by filtration. Fifty c.c. of the filtrate are placed in an Erlenmeyer flask and titrated with the N/10-NHSCN (solution No. 2) over a white background. The end-point is the appearance of a permanent reddish-brown color in the solution, due to the production of ferricyanate when all the silver has been precipitated.

The number of c.c. of N/10-NHSCN used in this titration is identical with the number of c.c. of N/10-$AgNo_3$ present in half of the filtrate from the precipitated silver chlorids. Twice this number equals therefore the total excess N/10-$AgNO_3$ in c.c. and this subtracted from 20 c.c. (the total amount of N/10-$AgNO_3$ used) gives the number of c.c. of N/10-$AgNO_3$ precipitated by the chlorids present in 10 c.c. of urine. Each c.c. of N/10-$AgNO_3$ is the equivalent of 0.00585 gm. of NaCl. If, for example, 8 c.c. of N/10-$AgNO_3$ were shown to have been

precipitated by the chlorids present, then $8 \times 0.00585 = 0.0468$ gm. NaCl were present in the 10 c.c. of urine. From this the total 24-hour output is easily calculated.

This method of Lüttke-Martius or the original Volhard method should be employed in all exact metabolic studies requiring determinations of chlorids.

2. *Simplified Chloridometry (Strauss, Bayne-Jones)*

Principle.—A simplification of the technic of this method has been introduced by H. Strauss, and his method has in turn been improved by Bayne-Jones.

The filtration of the precipitated chlorids is omitted, and the titration of the excess $\frac{N}{10}$-$AgNO_3$ is carried out in an ordinary (accurately calibrated) 50 c.c. graduated cylinder. Five c.c. of urine and 10 c.c. of N/10-$AgNO_3$ are placed in the cylinder and the excess $AgNO_3$ then titrated with N/20-NH_4SCN. The reading of the level of fluid in the graduate at the end of the titration gives, on comparison with a special table, the amount of sodium chlorid in grams. The method is sufficiently accurate for all clinical purposes.

In the following table is a scale showing the number of grams of chlorids per liter of urine, or of solution, tested as read off from the total amount of fluid present in the graduated cylinder at the end of titration (Bayne-Jones).

Scale for Chlorids (Bayne-Jones)

Chlorids Gm. per Liter	Volume	Gm.	Volume	Gm.	Volume	Gm.	Volume	Gm.	Volume	Gm.	Volume
0.0	35.000	2.0	31.58	4.0	23.16	6.0	24.74	8.0	21.32	10.0	17.90
0.1	34.829	2.1	31.409	4.1	27.999	6.1	24.569	8.1	21.159	10.1	17.739
0.2	34.671	2.2	31.238	4.2	27.828	6.2	24.398	8.2	20.988	10.2	17.568
0.3	34.487	2.3	31.069	4.3	27.657	6.3	24.227	8.3	20.717	10.3	17.397
0.4	34.316	2.4	30.896	4.4	27.486	6.4	24.056	8.4	20.546	10.4	17.126
0.5	34.128	2.5	30.72	4.5	27.30	6.5	23.88	8.5	20.48	10.5	17.04
0.6	33.971	2.6	30.549	4.6	27.129	6.6	23.709	8.6	20.309	10.6	16.869
0.7	33.803	2.7	30.378	4.7	26.958	6.7	23.538	8.7	20.138	10.7	16.698
0.8	33.632	2.8	30.207	4.8	26.787	6.8	23.367	8.8	19.967	10.8	16.527
0.9	33.461	2.9	30.036	4.9	26.616	6.9	23.196	8.9	19.796	10.9	16.356
1.0	33.29	3.0	29.87	5.0	26.45	7.0	23.03	9.0	19.625	11.0	16.19
1.1	33.119	3.1	29.699	5.1	26.279	7.1	22.869	9.1	19.454	11.1	15.919
1.2	32.948	3.2	29.528	5.2	26.108	7.2	22.698	9.2	19.283	11.2	15.748
1.3	32.771	3.3	29.357	5.3	25.937	7.3	22.527	9.3	19.112	11.3	15.577
1.4	32.606	3.4	29.186	5.4	25.766	7.4	22.356	9.4	18.941	11.4	15.406
1.5	32.435	3.5	29.025	5.5	25.605	7.5	22.175	9.5	18.755	11.5	15.33
1.6	32.264	3.6	28.854	5.6	25.434	7.6	22.004	9.6	18.584	11.6	15.171
1.7	32.093	3.7	28.683	5.7	25.263	7.7	21.833	9.7	18.413	11.7	15.000
1.8	31.912	3.8	28.512	5.8	25.092	7.8	21.662	9.8	18.242	....	.....
1.9	31.741	3.9	28.341	5.9	24.921	7.9	21.491	9.9	18.071	....	.....

Where only a small amount of urine (say 1 c.c.) is available, as in tests of function on ureteral catheterization, the amount should be diluted with distilled water to yield somewhat more than 5 c.c., and the determination made as usual, correcting for the dilution. Determinations made with small cylinders (10 c.c. size) are too inaccurate to permit of their use (Bayne-Jones).

3. Chloridometry in Small Amounts of Urine and of Other Body Fluids (McLean and Van Slyke)

Technic.—If protein is present, it must be removed, just as in examining blood. The chlorids are titrated in the protein free filtrate.

This method of McLean and Van Slyke is very useful in the determination of chlorids in urine obtained by ureteral catheterization in tests of renal function. It is also an excellent method for studies of blood. The method is fully described, together with the composition of the reagents employed in Part VII (*q. v.*).

4. Titration of Chlorids by Mohr's Method

This depends upon the principle that in a solution containing both chlorids and potassium chromate, to which a solution of silver nitrate is gradually added, the chlorids will all be precipitated as white silver chlorid before chromate of silver begins to come down as a red precipitate (end-reaction).

The method is inaccurate for the readings are too high. If used at all, any albumin present must first be removed, and one must rule out the presence of other halogens (iodids; bromids) since they are also precipitable by $AgNO_3$.

I advise the use neither of this method nor of the simplification of it introduced by Achard and Thomas.

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(*b*) *Phosphates* (P_2O_5)

The excretion of phosphorus in the urine is expressed in terms of P_2O_5. The normal excretion of P_2O_5 averages 3.5 grams daily.

i. Sources, Distribution and Excretion of Phosphates

The phosphorus in the *food* is in the form both of its inorganic salts and of its organic compounds: phosphorized lipoids, phosphorized proteids and nucleoproteids. These organic compounds are largely broken down by the processes of digestion, and the phosphorus set free as inorganic phos-

phates. According to the present view (Taylor, Grosser), phosphorus is resorbed from the intestine in the inorganic state.

The extent to which phosphorus is *resorbed* varies between 50 and 90 per cent of the phosphorus of the diet. A calcium rich diet predisposes to a diminished absorption, probably because of the formation of comparatively insoluble calcium salts.

The rôle of phosphorus in the *metabolism* of the body is not fully known. It is found in organic combination in the nucleic acid portion of the nucleoproteids, in the phosphorized lipoids, and in the form of a complex organic salt in the circulating fluids. Inorganic phosphates are found in the bones and in the blood.

The *excretion* of phosphorus is through the kidneys and intestinal tract. Usually the larger portion is found in the urine, but occasionally the reverse is true. A large amount of calcium or magnesium in the diet may lead to an increase in the phosphorus in the stools. In lactation, phosphorus is excreted in the casein of the milk. There is no phosphorus excreted through the skin.

ii. The Phosphorus Balance of the Body

A phosphorus balance *in health* is easily attained. The daily needs are covered by an intake of 1-2 grams of phosphorus (Ehrström). With an increase of the phosphorus intake above normal the body shows a tendency to retain phosphorus. In phosphorus starvation, on the other hand, the excretion of phosphorus continues. The inorganic phosphorus of the bones is drawn upon before the more stable lipoids and nucleoproteids (Masslow). During periods of growth, and in pregnancy, the phosphorus balance is negative.

The data as to the *pathological variations* in the phosphorus balance are rather inconclusive.

Ossification and Calcification.—The relation of phosphates to the processes of normal and abnormal ossification and calcification has been the subject of much work. In calcified areas, and in normal bone, calcium phosphate and calcium carbonate are found in a definite proportion to each other, which may be expressed by the formula $3(Ca_3(PO_4)_2) : CaCO_3$ (Hoppe-Seyler). In the blood, Barillé has shown the existence of a soluble complex double salt—tribasic calcium-carbon-phosphate ($P_2O_8Ca_2H_2 : 2CO_2(CO_3H)_2\ Ca$)—which is precipitated, when the CO_2 tension is lowered, as a mixture of calcium carbonate and calcium phosphate, in the proportions indicated in Hoppe-Seyler's formula. It is probable that, both in normal ossification and in pathological calcification, such a precipitation from the blood occurs. In *rickets* there is failure on the part of the osteoid tissues to calcify. It cannot be said that the cause of this failure is as yet fully determined. The calcium and phosphorus balances have

both been shown to be frequently negative in this condition, and, experimentally, either calcium or phosphorus starvation will produce bone changes similar to those of rickets. These data have, however, been questioned by other workers. In *osteomalacia* there is a great reduction in the proportion of inorganic salts in bone, but no details as to the defect in tissue metabolism are known. The calcium balance is negative. There is a high excretion of phosphoric acid through the feces.

Lipoids of the Nervous System.—A considerable proportion of the organically combined phosphorus in the body is in the form of phosphorized lipoids. As these lipoids are especially abundant in the structure of the central nervous system, it might be expected that, in nervous diseases, abnormalities of the phosphorus balance would occur. There is, however, very little known on this subject. The rôle of the lipoidal substances in activating body ferments and in the processes of immunity is but recently attaining recognition. The rôle of phosphorus in the metabolism of these bodies acquires by this an added interest.

Nucleic Acid.—In general, however, the metabolism of bone tissue, and of the lipoid rich tissues of the central nervous system, maintains itself at a very constant level, and, consequently, variations that occur in phosphorus output, on a constant intake, are usually due to variations in the intensity of nucleic catabolism, so that the phosphorus and the purin output tend to run parallel. In gout the phosphorus excretion follows the curve of the uric acid elimination. It is probable that the abnormalities in the phosphorus output that have often been observed in thyroid disease are attributable to the disturbances of purin metabolism, now known to accompany that condition.

iii. Phosphatic Diabetes and Phosphaturia

The term phosphatic diabetes has been applied to cases showing many of the symptoms of diabetes, without glycosuria but with an increased phosphorus output in the urine.

The kidney in nephritis retains phosphoric acid and its salts. This *P-retention*, according to Purdy, is a very constant factor in both acute and chronic nephropathies.

In the urine almost all of the phosphorus is in inorganic form as salts of the tribasic orthophosphoric acid (H_3PO_4). Only about 1 per cent is excreted in organic form (probably as glycerophosphoric acid). About two-thirds of the phosphoric acid in the urine is combined with sodium and potassium, about one-third with calcium and magnesium.

Monosodium phosphate, (NaH_2PO_4), is an acid salt; disodium phosphate, ($Na_2H\ PO_4$), neutral; and trisodium phosphate, (Na_3PO_4), alkaloid. The elimination of the acid salt is one of the most important

methods the body possesses of ridding itself of excess H-ions; and the preponderance of this salt in the urine is the cause of the greater part of the normal urinary acidity (*q. v.*).

Considerable interest has attached to the voiding, either constantly or in attacks, of urine cloudy with precipitated phosphates. The name *phosphaturia* has commonly been applied to this condition, which, it is said, is frequently associated with functional nervous disease. There is, however, no increased phosphate excretion in this condition. The calcium excretion, on the other hand, is increased in the urine and diminished in the stool. Hence the proportion of calcium to phosphates in the urine is greater than the average. Moreover, there is a lessened excretion of the acid salt of phosphoric acid, and a tendency to an amphoteric, or an alkaline, reaction of the urine. All these are favorable conditions for the precipitation of calcium phosphate crystals. But, according to Lichwitz, the determining factor in the precipitation is to be found in an ether soluble protective colloid. Its presence explains the lack of phosphate precipitation in some alkaline urines, rich in calcium phosphates, while in *phosphaturia* it is because this colloid tends to go out of solution in the formation of the surface scum that precipitation of the phosphates throughout the body of the solution occurs. Lichwitz considers that the essential etiological factor in phosphaturia is a renal abnormality, that leads to continued secretion of alkaline urine, with corresponding retention of H-ions. It cannot be said that this condition of phosphaturia has as yet attained a place as a clinical entity.

iv. Quantitative Determination of Phosphates in the Urine

The value of this determination is at present confined to metabolic researches. Only from careful measurements of output in stool and urine on a controlled intake can any inferences of value be drawn. The quantitative estimation of phosphates in an ordinary specimen of urine, so often asked for and obtained, is absolutely worthless by itself. It seems unnecessary, therefore, to give the methods for quantitative determination here. For exact metabolic studies, determinations of phosphoric acid may be necessary, and then the *ammonium molybdate method* of Neumann (see References) may be employed. Direct determination by means of the *uranium acetate method* as used by Salkowski and Thierfelder is simpler and more rapid, but less exact.

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(c) *Carbonates*

Salts of carbonic acid (H_2CO_3) are usually present in only small amounts in normal acid urine; they may be present in larger quantities in neutral or alkaline urine, especially when the number of cations (Na, K, Ca, Mg) is increased by a vegetable and fruit diet, which is rich in such cations, or after drinking alkaline mineral waters, or taking large doses of sodium bicarbonate. Under these conditions a precipitate of amorphous calcium carbonate is common. The determination of carbonates in the urine is of no clinical interest.

(d) *Sulphates (SO_3) and Other Sulphur Compounds*

i. Sources, Distribution and Excretion of Sulphates

The *average output* of sulphur in the urine, calculated as SO_3, is about 3.5 gm. a day.

In the *diet,* sulphur occurs both as inorganic sulphates and as sulphur in organic combination. The organically combined sulphur is found chiefly in protein, but to a slight extent in fat. The protein sulphur is contained in the amino-acid, cystin.

Cystin, the sulphurized fat, and inorganic sulphates are *resorbed.* The sulphur resorbed in the last two substances is excreted. Only the sulphur of the amino-acid, cystin, is of use to the body in the synthesis of the various sulphur-containing substances of the tissues. To this synthetic use is therefore put as much of the resorbed amino-acid sulphur as is needed. The excess cystin is catabolized, and its sulphur goes into the form of sulphates. The sulphur of sulphurized fat is likewise oxidized to sulphate form.

From the resorbed sulphur of the diet, therefore, there are derived *sulphates* and various synthetically formed *sulphur-containing bodies* in the tissues. The catabolism of these tissue constituents yields in part sulphates, and in part, where oxidation is less complete, organically-bound sulphur (neutral sulphur).

The sulphates thus derived in part from the diet directly and in part from the catabolism of tissue constituents, and the organically bound sulphur, derived from less complete catabolism of tissue constituents, all are *excreted,* in the urine, the feces, and the sweat.

The sulphates in the urine are in part combined with inorganic cations (K Na Mg), and in part with aromatic radicles resorbed from the intestines. The first fraction is termed *inorganic sulphates,* while to the second the term *aromatic,* or *ethereal, sulphates* is applied (*vide* Aromatic Compounds in the Urine).

The *neutral sulphur* in the urine is chiefly contained in bodies which represent incompletely catabolized cleavage products of protein—the oxyproteic acids (*q. v.*). The variations in this fraction of the sulphur output are chiefly due to the variable amounts of the oxyproteic acids produced. Occasionally, however, a very great increase in the output of neutral sulphur is associated with the excretion of cystin (*vide* Cystinuria). The other constituents of the neutral sulphur fraction are of less importance.

ii. Quantitative Determination of the Sulphur Bodies in the Urine

These methods yield data of value only as a part of a metabolic research.

To determine the free and the conjugated (ethereal) sulphates, the method of E. Baumann (1877) may be employed. To determine the sulphur in dried residue (urine or feces), the method of Folin (1906) may be used either for inorganic sulphates or for total sulphates. To determine the total sulphur of urine, Denis' modification of Benedict's method can be recommended. The total sulphur and the total phosphorus may be estimated by the method of Wolf and Osterberg (1910). (See References.) The methods are described in C. Neuberg's *Der Harn.*

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II. INORGANIC CATIONS

(a) *Calcium* (*CaO*)

i. Sources, Distribution and Excretion of Calcium

The *average daily output* of calcium in the urine calculated as CaO, varies between 0.33 and 0.80 gram. The excretion in the feces is, however, of equal importance; so that all investigations of calcium metabolism must include determinations of the excretion in both stools and urine.

Calcium is present in the *diet* in inorganic form as carbonate, sulphate, or phosphate and also in more complex organic combinations, in milk, egg yolk, grain, etc.

Resorption of calcium salts is no doubt largely dependent upon the solubility of these salts under the conditions present in the intestines. The calcium carbonates and phosphates are soluble in an acid media but are precipitated in alkaline solution. To this fact may be due the greater absorption of calcium which is noted after the administration of mineral acids. It has been shown that where the amount of phosphates in the diet is high, the resorption of calcium salts is much impaired, and the proportion of both calcium and phosphorus in the stools is increased. Various forms of enteritis are said to markedly influence calcium resorption. Definite data are not obtainable, however, for it is impossible to separate in the feces the unresorbed calcium from the calcium excreted into the intestines.

Calcium salts are *excreted* in varying proportions in the urine and feces. Of the total output the urine contains, according to different investigators, from five to fifty-five per cent. The factors that determine the pathway of excretion are not well known. The pediatricians have shown that an alkaline reaction in the large intestine, with a high content in soaps, leads to an increase of calcium excretion by this route.

The *distribution* of calcium in the body, and the rôle it plays in normal tissue metabolism, are very incompletely known. The bones are evidently the main storage depot of inorganic calcium, which is found in them as a mixture of phosphates and carbonates in the proportion shown by the formula 3 $(Ca_3(PO_4)_2)$: Ca CO_3, (Hoppe-Seyler). This ratio of calcium phosphate to calcium carbonate is also found, according to Barillé, in the blood where the two salts are combined in a soluble complex double salt. In various organs a percentage of calcium is found

that is fairly constant for each organ; and in the brain the variations in this calcium content have been shown to be related to functional disturbances.

ii. The Ca Balance of the Body

Calcium balance in the body is not easily determined. When calcium salts are fed, the body retains them over long periods (Voorhoeve). On the other hand, in starvation the excretion of calcium is increased above normal, apparently because of dissolution of bony tissue. In general it may be said that *in health* an intake of 1.0–1.5 gms. CaO is sufficient to maintain the adult body in calcium balance.

Under *pathological conditions,* the behavior of the calcium metabolism is often of interest.

Ossification and Calcification.—This is especially true in diseases connected with defective ossification or with pathological calcification, *e. g.,* rickets, osteomalacia, arteriosclerosis, etc. In bone and in calcified areas alike, calcium occurs almost entirely in the form of phosphates and carbonates in the same proportion in which Barillé has found them to exist in the blood (*vide supra*). The factors that control the precipitation of these salts in the tissues to form bone or areas of calcification and the factors that determine the resorption of these salts from bone are incompletely known. Their existence in solution in the blood Barillé has shown to be dependent upon constant maintenance of the CO_2 tension at a certain level. The areas in which calcium precipitation occurs are characterized physically by their homogenous hyaline structure. It is probable that these areas have a specific absorption affinity for the calcium salts of the blood; such as is experimentally known to be possessed by certain colloids. Hofmeister suggests that, following such absorption, a decrease of the CO_2 tension in the tissue would be accompanied by a precipitation of calcium salts, which would renew the power of the tissue to absorb more calcium. Wells tends to see in such physicochemical factors and in variations in CO_2 concentration the most reasonable explanation at present available of the processes of ossification and calcification. On the other hand nothing is known of the factors controlling the resorption of calcium salts from bone, such as occurs in many conditions.

Aside from possible defects in the immediate processes of calcification and ossification, more remote causes of abnormalities in these processes must be sought in possible deficiencies in the mineral intake, in the calcium resorption, and in the ability to retain calcium. As a result of the difficulties in controlling the many possibilities, very little is yet definitely known of the causes at work in these cases.

Rickets is characterized by a poverty of the bones in inorganic salts with arrested and imperfect ossification. Extensive investigations have as yet led to no agreement as to the cause of this condition. By some

a local deficiency in the osteoid tissue is held to explain the abnormal ossification. But, more recently, evidence of increased calcium excretion in the stools, and of a tendency to a negative calcium balance, has been secured (Dibbelt). This has encouraged certain investigators to attribute rickets to calcium starvation (Schabad). In *osteogenesis imperfecta* a similar negative calcium balance has been observed (Schabad, Bookman).

In *osteomalacia,* as in rickets, the content of the bones in calcium salts is much diminished, but this diminution is due to resorption of the salts, and not, as in rickets, to failure in the processes of ossification. During the active stage of the disease the calcium output is increased, and the calcium balance is negative. If recovery occurs this is followed by a stage of marked calcium retention (Neuman).

The behavior of the calcium metabolism in *tuberculosis* has been studied especially by French observers, who have stated that there occurs characteristically in this disease a demineralization that affects the calcium content of all tissues, except the lungs, in which on the contrary the calcium content is increased. An inability to retain mineral bodies and a tendency to a negative mineral balance exist in certain persons and have been elevated to the rank of a diathesis. The subjects of this diathesis are held to be predisposed to tuberculosis. Evidence in favor of this hypothesis is very incomplete. Voorhoeve has recently shown, however, in a carefully controlled metabolic study, that in certain cases of tuberculosis, selected to exclude disturbing factors, there did appear a disturbance of calcium retention so that a definitely increased calcium intake was needed to keep the patient in calcium equilibrium.

In *tetany,* due to parathyroid extirpation, MacCallum and Voegtlin found an increased elimination of calcium with an accompanying decreased content of calcium in the blood and brain. They were able to alleviate the symptoms by intravenous administration of calcium lactate. It has been shown (J. Loeb) that calcium does diminish nervous irritability. Moreover, the parathyroidectomized animals may show disturbances of dentition and of bone repair. It seems probable, therefore, that the parathyroid glands exert an influence upon calcium metabolism. But since others have failed to confirm the work of MacCallum the results of further investigation must be awaited.

In the urine, the calcium is in the form of phosphates chiefly, and only to a lesser extent appears as carbonates, sulphates, urates and oxalates. It often forms mixed salts with magnesium. The calcium excretion in the urine bears a certain relation to the ammonia excretion, since both depend to some extent upon the amount of acid to be neutralized in the body.

The variations in calcium excretion in *phosphaturia* are mentioned under that heading.

iii. Quantitative Determination of Calcium in the Urine

The methods are not clinically applicable at present. Only by complete calcium balance investigations can data of value be obtained (consult references and larger hand-books). It is usually advisable to combine in such an investigation determinations of the closely allied magnesium and phosphorus balances.

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Zur Lehre des Kalkstoffwechsels. 3. Calcarurie. Deutsches Arch. f. klin. Med., Leipzig, ***1913,*** *cxi, 29–46.*

(*b*) *Magnesium* (*MgO*)

The *average daily output* of magnesium in the urine amounts to 0.2–0.3 gm. calculated as MgO.

Magnesium is *resorbed* chiefly from the small intestine and is excreted partly in the urine and partly in the stool. It is found in the body in the same situations as calcium, in much smaller amounts, however, and chiefly in the form of $Mg_3(PO_4)_2$. In bone, magnesium makes up about 10 per cent of the total ash, and stands in the relation to calcium of 1:8.5–9.

In the *urine,* magnesium is found chiefly in the form of phosphates. (For *methods of determination* of Magnesium, consult the following references and larger hand-books).

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(c) Sodium (Na_2O) and Potassium (K_2O)

These metals are excreted in the urine in amounts varying, for sodium, between 4 and 7.5 grams, and for potassium, between 2 and 4 grams, calculated as Na_2O and K_2O respectively.

In the *diet,* the proportions of sodium and potassium vary according as vegetable or animal food predominates. In animal food, according to Bunge, the proportion of sodium to potassium salts is approximately that required by the human body; while in vegetable food, sodium is present in proper amounts, but there is a disproportionately large quantity of potassium salts. Most of the sodium is present in the form of sodium chlorid and most of the potassium as potassium phosphate. The reaction between these two bodies yields sodium phosphate and potassium chlorid. According to Bunge, the custom of adding salt (NaCl) to vegetable food, is due to the need of maintaining a certain proportion of sodium to potassium salts so as to ensure proper equilibrium in the reaction between them in the body.

In the *body* sodium salts are found chiefly in the circulating media; while potassium compounds are held for the greater part in the fixed tissues.

The relation of these mineral constituents to the function of tissues has been brought out in recent years. In muscle contraction, for instance, sodium plays a necessary part; while to some extent potassium acts as an antagonist to this function. Potassium exerts a depressant effect upon the myocardium. Vagus inhibition increases the potassium content in the blood of the coronary veins; the mechanism of this specific action of potassium is, however, unknown. Growth has been shown to bear a relation to the relative proportions of potassium as compared to calcium in the tissues. Clowes and Frisbie found that in rapidly growing tumors a high percentage of potassium is found and little or no calcium, whereas in old slowly growing tumors the relation is reversed. In diseases in which tissue destruction occurs, there is an increased potassium output in the urine.

Sodium excretion tends to follow the chlorid excretion in conditions where the latter shows abnormalities, as, for example, in pneumonia.

Both sodium and potassium play an important part as cations in the neutralization of acids in the body. In this function they are supplementary to the ammonia derived from the deaminization of amino-acids.

The *excretion* of sodium and potassium is chiefly through the kidneys. The feces, sweat, sputum, etc., contain, however, appreciable amounts.

The *quantitative determination* of these bodies is at present of no clinical significance. For the methods employed in exact metabolic studies of sodium and potassium, the references appended may be consulted.

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(*d*) *Iron* (Fe_2O_3)

The *average daily excretion* of iron in the urine is 1 milligram. (Neuman and Mayer).

In the *diet,* iron is present as inorganic salts, especially in drinking water, and as organic compounds of iron (casein in egg-yolk). Spinach, among the vegetables, and blood sausage in the animal foods, are the richest in iron content.

The details as to the *resorption* of iron are still undetermined. It may be assumed as proven, however, that iron in organic or inorganic state, undergoes more or less complete resorption in the small intestine.

The human *body* contains about 3.2 grams of iron, of which 2.4 to 2.7 grams are in the blood (Wells). The iron in the blood is contained in the red blood corpuscles as a constituent of the hemoglobin. *Blood pigments,* which play a rôle as carriers of oxygen in the internal respiratory exchange, are common to all vertebrates and are all characterized by containing a heavy metal in organic combination. The metal is usually iron, but occasionally copper, and in one instance, vanadium has been found occupying this position. The oxygen carrying power of the blood pigment is associated with the metal it contains. Iron thus plays an important part in oxidative processes both inside and outside the body. *Oxyhemoglobin* contains a constant percentage of iron, 0.32–0.34 per cent.

The details of the *metabolism of iron* are not clearly known. Resorbed iron from the diet, as well as iron derived from the breaking down of hemoglobin, in part is stored in the liver, the spleen, the muscles and in other tissues; in part it is used in the synthesis of new hemoglobin, and in part is excreted in the stools and in the urine. The excretion, however, is small and probably does not indicate the activity of the interchange of iron inside the body. Since the body thus stores most of the iron set free instead of excreting it, only a very small intake is necessary to maintain iron balance in the body. For an adult this amount has been estimated at 0.06 gram a day.

The *excretion* of iron is chiefly into the large intestines while only a milligram or so is eliminated in the urine, in the form of chromogens and other organic combinations.

Quantitative determinations of the iron excretion are at present of no diagnostic value.

D. Methods of Examining the Urine for Abnormal Constituents

1. The Significance of Abnormal Constituents of the Urine

The division of this section into parts dealing respectively with the normal and abnormal constituents is a measure taken in the interests of the clinical utilization of the material. As a matter of fact, the distinction between normal and pathological is as often based upon the amount of the substance present in the urine as upon its chemical individuality.

Many of the substances to be discussed in this section, such as *d*-glucose, are present in small amounts in normal urines; while, as has already been seen, many normal constituents of the urine show pathological quantitative variations in disease.

The appearance of abnormal urinary constituents may be accounted for as a result of some one of the following conditions:

(a) The formation in metabolism, or the resorption of some abnormal body, which is excreted by the kidney.

(b) The accumulation in the blood of some normal metabolic product in excess of normal amounts, with consequent excretion.

(c) Disease of the kidney, or of the genito-urinary passages.

(*a*) *Excretion of Substances Not Normally Present in the Body*

A vast deal of work has been done in the past in attempts to connect certain bodies in the urine with certain diseases. A brief review, therefore, of the production by the body of specific substances under the conditions of disease and of the excretion of such bodies in the urine would seem desirable.

It is comparatively rare that, in disease, tissue constituents are formed that, by our present chemical and physical methods, can be shown to be distinct from those occurring in health. Though the histological structure of pathological tissue may be abnormal, the synthesis of protein, of fat, and of carbohydrate that occurs in the formation of the protoplasm of these pathological tissues (such as tumors), apparently results in proteins, fats, and carbohydrates similar, in as far as chemical characteristics go, to those of normal tissues. That, for the proteins at least, a certain *specificity* may exist, not detectable by the present physicochemical methods, is entirely probable in view of the high degree of individuality of the protein bodies that a study of their immunological properties has revealed. But, not to go too far afield, the general observation holds true that, in spite of very diligent search, only a very small number of specific bodies, synthesized in disease only, and not constituents of normal tissues, have been found. As a consequence, abnormal constituents of the urine, of such specific nature and significance are, thus far, few in number. A striking exception to this last statement lies in the occurrence of the *Bence-Jones protein;* though formed in the body in disease (*e. g.*, as a constituent of myelomas), and excreted in the urine, it is never found in normal urine nor in normal tissues. It is a foreign protein.

Certain bacteria growing within the body (bacilli of tetanus and of diphtheria) produce *soluble toxins* that may be looked upon as specific substances, produced within the body as a result of disease, probably of the nature of proteins. These toxins cause, in turn, the production within the body of equally specific substances known as *antitoxins*. This

formation of antitoxin may be taken as an example of the power of the body to produce, in disease, substances known as *antibodies*, which are not found in the normal body, and which, to a greater or less extent, are specific. The excretion of such substances in the urine is probably very slight, however, and up to the present, has not been put to any diagnostic use.

This similarity of the anabolic processes in disease to those in health, finds its counterpart in *catabolism,* which, in disease, yields the same degradation products as does normal catabolism, though often in different proportions. This variation in proportions often leads to the accumulation of some body in the blood in excess of the amount usually present therein, and, then, to its excretion in the urine. But such a body need not be the result of a specific type of catabolism. It is probably true that in all the pathological processes in which catabolism of tissue constituents occurs, whether it be (1) the wasting of the normal tissues in disease, (2) the autolysis of pathological cells (in tumors, exudates, etc.), or (3) the bacterial digestion of tissue, the types of cleavage products are only quantitatively abnormal. Hence no specific chemical substance results.

The case is somewhat different when we consider the results of the catabolism in the body of *parenterally introduced foreign proteins* as opposed to catabolism of autogenous protein, referred to in the preceding paragraph. It is, indeed, not proven that the cleavage bodies resulting from the action on this foreign molecule of the proteolytic ferments of the blood or tissues are qualitatively different from the split products of autogenous protein molecules; but, it is fairly well proven that one of these cleavage products of foreign protein is toxic, producing the symptoms termed *anaphylaxis.* Hence the cleavage of foreign protein must result either in the production of a qualitatively abnormal substance, which seems more likely, or (because of quantitative variations in the proteolysis), a great excess of some normal product, toxic when present in large amounts, is produced. At any rate, the regularity of the occurrence of anaphylaxis under certain conditions, and the uniformity of the symptoms, points to a single cleavage product as the cause. To this hypothetical body, the chemical nature of which is as yet not certainly determined, the name *anaphylatoxin* has been given (see Part IV). Pfeiffer states that, during anaphylactic intoxication, poisonous substances, similar to anaphylatoxin, appear in the urine.

By the action of certain putrefactive bacteria, *qualitatively abnormal bodies* are produced which, since they may appear in the urine, are of interest here. The putrefaction of the aromatic amino-acids (tyrosin, phenylalanin, etc.) produces *indol, skatol,* etc., the action on certain amino-acids results in the production of substitution products of ammonium, the *ptomains.* These chemical reactions do not occur under the

influence of the normal enzymes of the body. Hence, when their end-products, resorbed from the intestines, or, under special conditions, formed within the body itself, are excreted in the urine, their appearance there is diagnostic of the occurrence of bacterial fermentative processes.

Other abnormal substances that have a specific significance, occurring in the urine, include various *drugs, poisons,* and *other foreign substances* that are excreted by this path.

(*b*) *Excretion of Substances Not Abnormal in Themselves but Present in the Blood in Abnormally Large Amounts*

The accumulation in the blood of some normal metabolic product, which, usually, is not present in sufficient amounts to ensure excretion by the kidneys, is a commoner cause of the appearance in the urine of abnormal constituents.

The chief normal urinary constituents are *end-products* of metabolism. Most of the *intermediary products* are not present in sufficient concentration in the blood to ensure excretion by the kidney. But, if one form of metabolic process be markedly increased, the intermediary products in that form may appear in the urine. Thus, for instance, in excessive protein-catabolism as in the sudden autolysis of a pneumonic exudate, many of the degradation-products of protein (*albumoses, peptones, polypeptids, amino-acids*) may appear in the urine. Similarly, abnormal concentration of intermediary bodies in the blood may occur when there is a slacking up, at one stage, or an actual arrest of the catabolism of some substance. For instance, when the utilization of *glucose* is abnormally limited (as in diabetes mellitus), hyperglycemia and glycosuria result. Again, the appearance of *creatin* in the urine is due, in the same way, to accumulation in the blood, resulting from a failure in the anhydration process by which it is normally changed to creatinin. Defects in the intermediary oxidations of fat in acidosis result similarly in the accumulation and the elimination of *beta-oxybutyric acid.* It is evident that too great stress can scarcely be laid upon the importance of this type of metabolic defect as a cause for the appearance of abnormal bodies in the urine.

(*c*) *Appearance of Abnormal Substances in the Urine as a Result of Disease of the Kidneys or of the Urogenital Passages*

The abnormal constituents of the urine to which most attention has, hitherto, been paid, clinically, are those that are associated with disease of the kidneys or of the genito-urinary passages, such as *albumin, red blood corpuscles, leukocytes* and *casts.* In discussing the other two main classes of abnormal constituents, it has been assumed that the renal func-

tions were normal. The nature of the disturbances of renal function will be discussed in Part X. Generally speaking, pathological changes in the kidneys tend usually toward a diminished excretion of the *crystalloid bodies* in the urine, while certain *colloids* (serum albumin and serum globulin), which are abnormal constituents, appear (*vide* Part X). Products of inflammation, fibrin, red blood corpuscles and leukocytes may appear in the urine in affections of the genito-urinary tract.

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2. Coagulable Proteins in the Urine

The *general chemistry of proteins* is summarized in Part XIII. To understand the excretion of proteins and protein degradation products in the urine, it is necessary to remember that the *source* of most of these substances is the blood.

The blood carries in its plasma certain proteins, often called the "stock proteins" of the body, since it has been supposed that from the constituents of these proteins the tissue cells were able to synthesize all the special proteins of the body. These "stock proteins" are serum albumin, and serum globulin. Besides these the plasma contains other less important proteins such as fibrinogen, fibringlobulin, glutolin and serum-mucoid. Moreover, all the *intermediary bodies* in the catabolism of protein may be found in the blood, and all the end-bodies of protein catabolism are normal blood constituents. Finally in the red blood corpuscles there is contained a special chromoproteid, hemoglobin, which may, under special circumstances, be set free in the plasma, so that hemoglobin or derivatives of hemoglobin may appear in the urine. It is possible that the ingestion of an excessive amount of *foreign protein,* such as egg albumen, may lead to the absorption of this protein unchanged into the blood and its excretion into the urine. An *abnormal protein formed in disease* will likewise be carried by the blood to the kidneys. Another source of urinary protein may be the *kidney* itself. The possibility exists, though unproven, that in renal disease the kidney excretes protein derived from its own tissue cells. An *inflammatory exudate* (in cystitis, ureteritis, etc.) may add protein constituents to the urine.

From these various possible sources, foreign protein of the diet, for-

eign protein formed in disease, blood proteins (serum albumin, serum globulin, hemoglobin), intermediary products of protein metabolism, end-products of protein metabolism, hypothetical kidney tissue proteins, proteins of inflammatory exudates, are drawn the proteins and protein degradation products that are found in the urine in health and in disease.

In *health,* the urine contains end-products of protein catabolism, while in *disease,* the commoner pathological constituents are certain proteins (serum albumin, serum globulin, fibrin, Bence-Jones body, hemoglobin), and certain intermediary substances in protein metabolism (albumoses, polypeptids, amino-acids). These pathological constituents are roughly grouped for discussion, according to certain chemical characteristics. The soluble proteins that are found in the urine are *coagulable* by various procedures. Such are serum albumin, serum globulin, fibrinogen, Bence-Jones protein and hemoglobin. The less hydrolyzed intermediary bodies (albumoses, peptones), though no longer coagulable, still yield a *biuret test,* which distinguishes them in turn from the *a-biuret substances,* peptids and amino-acids.

(*a*) *Serum Albumin and Serum Globulin*

i. Clinical Significance of Albuminuria

The study of the significance of these two bodies in the urine has been largely a clinical study. The relationships of albuminuria and renal function have furnished the chief interest in these substances.

The question of their derivation cannot be said to have been definitely settled as yet, but it is very probable that they are derived from the blood plasma.

Serum albumin and serum globulin are usually associated in the urine; although cases have been reported in which each one of these proteins has appeared separately. The proportionate amounts of these two bodies varies under certain conditions. In nephritis the globulin fraction is said to be greater the more acute the condition. In general, however, the significance of both bodies is so closely similar and their coexistence in the urine so constant that it is customary to test the urine only for serum albumin and to neglect the globulin fraction.

The clinical significance of albuminuria will be referred to only briefly in this place as it is discussed also in Part X, to which the reader is referred.

It is important to distinguish the cases of albuminuria of non-renal origin, the so-called *accidental albuminurias,* from those in which the albumin is excreted by the kidney. The albumin found in the urine in accidental albuminuria is due to admixture of inflammatory exudates, menstrual blood, lymph, spermatic or prostatic fluids, pus and other

extraneous material. The possibility of such a non-renal origin for the albumin present in the urine must always be considered; the presence or absence of red blood corpuscles, hemoglobin, pus cells, etc., will usually make a decision possible.

In the *true renal albuminurias,* the question of the greatest clinical interest is the condition of the kidney. A very minute trace of albumin is probably present in all urine, though this amount is too small to yield a positive reaction with the ordinary tests. Appreciable amounts may occur in perfectly normal persons after severe exertion, mental strain, cold baths, etc. Numerous types of so-called *functional albuminuria* in which there is presumably no true renal disease, have been described. An understanding of these conditions will be attained only when we have progressed further in our knowledge of the factors governing the mechanism of the excretion of albumin. One of the most interesting forms is the so-called *orthostatic* or *lordotic albuminuria.*

Other even commoner instances of albuminuria without true nephritis are those associated with febrile or toxic conditions, and those resulting from chronic passive congestion of the kidneys.

The urine of cases of *true nephritis,* almost invariably shows albumin, though in some rare instances none may be found on repeated examination. It must be strongly emphasized that in *chronic nephritis* and in the *arteriolar nephropathy* the amount of albumin bears no definite relationship to the severity of the process. In *convalescence* from acute nephritis the diminution in the albumin-content of the urine is often roughly proportionate to the improvement in renal function as shown by other tests.

The absolute amounts of serum albumin excreted in nephritis vary from a trace up to 40 or more grams per diem. From 3 to 6 grams of serum-albumin per diem may be regarded as a moderate pathological excretion.

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ii. Qualitative Tests for Albumin

Serum Albumin as a Protein

In general the tests for proteins are (a) color reactions, (b) precipitation reactions (see Part XIII).

The *color reactions* are due to the presence of certain chemical nuclei in most protein molecules, but as these groupings may be found in the degradation products of protein these tests are not specific for the protein molecule. The biuret test, for instance, is given by certain synthetically formed polypeptids.

The *precipitation reactions* likewise are not specific for the protein molecule since in certain of them albumoses, etc., are precipitated. But, by their means a separation of proteins and of protein degradation products into certain classes has been achieved. The nature of these precipitations is complex. It is dependent upon the colloidal nature of the protein solutions. Amphoteric colloids such as serum albumin may be thrown out of solution by adjusting the reaction of the media to a certain feebly acid point at which the ionization of the protein molecule is reduced to a minimum—the so-called *iso-electrical point,* which varies for each protein.

Certain chemical and physical influences tend to change the properties of the colloids, to *denature* them. Thus the cations of heavy metals, the strong mineral acids, the influence of heat all tend to denature serum albumin, so that it changes its properties, ceasing to be in a *sol* form, and assumes an insoluble *gel* form.

Neutral salts of the light metals ($MgSO_4$, Na_2SO_4, $(NH_4)_2\ SO_4$, NaCl) will also precipitate the colloidal solutions of proteins. No denaturation occurs in these cases, and the precipitated protein can be redissolved.

1. Heat and Acetic Acid Test for Albumin

Principle.—This test is not yet fully understood. All three of the above mentioned factors in the precipitation of colloid protein solutions

are made use of. The *reaction* of the urine is arranged to approximately the iso-electric point by the addition of small amounts of acetic acid, the protein is *denatured* by heat, and *precipitation* is favored by the neutral salts either present in the urine or added to it.

The test properly performed is quite delicate enough for all clinical purposes and is one of the most satisfactory in use. The test is said to reveal albumin in a dilution of 1:130,000 (Glaesgen).

Technic.—Unless the urine is *clear,* it is necessary to filter it. Simple passage through the filter paper will often be sufficient, but in the case of the fine haze due to bacteria the urine must be shaken with infusorial earth (Kieselguhr), or with powdered magnesium oxid, and the mixture then filtered through double folds of filter paper.

The urine must have an *acid reaction.* In case the specimen is found to be alkaline to litmus, a sufficient number of drops of 3 per cent acetic acid should be added to turn the reaction just acid.

A test tube (18–20 mm. in diameter) is filled three-quarters full with the clear acid urine, and the upper portion of the fluid heated to boiling over a small flame, the tube being held in the hand by its lower end. The boiled portion of the urine is then compared with the cool urine in the lower part of the tube. If a cloud has appeared in the heated portion, it may be due to a precipitation (1) of calcium phosphate or carbonate, (2) of albumin, (3) of both albumin and calcium salts. The decision is made by adding five or six drops of 3 per cent acetic acid to the urine and observing what happens. Calcium phosphate is dissolved; calcium carbonate is dissolved with effervescence; albumin is not dissolved by this amount of acid, in fact, the amount precipitated may be increased; a cloud due to both albumin and calcium salts is lessened by the acid but does not wholly disappear.

By careful attention to certain details of the test its delicacy is increased. A faint haze in the urine is easily overlooked unless the tube is held against a dark background, with the line of vision at right angles to the source of light. If the urine is of low specific gravity, the test will be more delicate if the deficiency in neutral salts be made up by the addition of one-sixth volume of saturated sodium chlorid solution (Purdy).

Sources of Error.—The test contains certain *sources of error* that must be guarded against.

1. If too much acid be added the albumin may be converted into the soluble acid albumin. Usually, however, a considerable excess of 3 per cent acetic acid must be added to cause a precipitate of albumin to redissolve. Experimentation with known specimens of urine best enables the worker to know what addition of acid is safe.

2. A faint cloud may be due, not to serum albumin, but to the so-called "nucleo-albumin" (*vide infra*). In such cases dilute acetic acid should be added to another test tube full of urine, in the cold. If a cloud forms it is due to "nucleo-albumin." This precipitate is removed by filtration, and the cleared urine is boiled as before described. If any cloud now appears on boiling, it is due to true albumin.

3. Following the administration of *cubebs, copaiba, turpentine, benzoin,* etc., resinous acids are excreted, which under the conditions of the test may produce a precipitate. This precipitate is differentiated from that due to albumin by its solubility in alcohol.

4. Albumoses are dissolved at boiling temperature. A cloud appearing during cooling of the urine may be due to albumose. It will redissolve on boiling. The

Bence-Jones protein (*q. v.*) is coagulated at about 60° C. but usually redissolves in part or wholly at the boiling point.

2. *Heller's Test for Albumin*

Principle.—The principle of this test is the *precipitation* of colloidal solutions of protein by strong mineral acids. The proteins are *denatured* and cannot be redissolved in water. The precipitated protein is usually soluble, however, in an excess of the acid. In the case of nitric acid, however, an excess will not redissolve the precipitate. By layering urine on concentrated nitric acid, a precipitation at the zone of contact ("ring test") is produced if albumin is present. By this test, albumin may be demonstrated in a dilution of 1:35,000 (Glaesgen).

Technic.—The urine must be clear, and acid in reaction. At the bottom of a conical glass, a few c.c. of concentrated nitric acid are placed and about double the amount of urine is allowed to run slowly down the side of the glass in such a way as to form a distinct layer of urine above the acid. It is important to obtain a clear-cut layering. The writer has found it convenient to fold a filter paper and to pour the urine slowly through the paper cone thus formed while this cone is held against the inside of the conical glass. The wetting of the filter makes it adhere to the glass and the filtrate trickles down the wall and layers itself very satisfactorily on the acid.

Albumin, if present, is precipitated *at the zone of contact* in the form of a white opaque ring. This ring is usually sharply defined at first; but upon standing it loses its distinct outline.

Sources of Error.—It is important that the site and the properties of the ring be carefully observed since the *source of error* in the test is the appearance of somewhat similar rings not due to albumin.

Below the site of the albumin ring, and tending to extend into the acid, it is customary to find a reddish violet transparent ring which is due to the reaction of the *normal urinary pigments* with the nitric acid. When abnormal pigments are present in the urine, such as *bile pigments, indican,* certain *drugs,* etc., a variety of colors may appear as a ring just below the junction of the acid and urine.

At the zone of contact of urine and acid, *albumoses* and *resins* may be precipitated either with albumin or alone. The ring due to resins, which are excreted after ingestion of certain drugs (copaiba, benzoin, etc.), will not appear if the urine be extracted with ether before it is used for the test. If the ring is due to albumose it will dissolve upon heating, while that due to albumin will remain.

Another ring at the site of the albumin ring is one that may be observed when the urine tested has been preserved with *thymol.* The ring itself is grayish white and "below the ring there is a greenish zone extending somewhat into the acid, above it a reddish, somewhat smaller zone." If this substance is suspected the urine should be extracted by shaking with an equal volume of petrolic ether.

More rarely, a distinctly crystalline ring appears at the zone of contact of acid and urine, due to the precipitation of *urea nitrate* in urines that are very rich in urea. If the urine be diluted, the ring fails to appear.

About 1 cm. above the zone of contact of acid and urine a cloudy zone, or a ring, may appear, due to the precipitation of *"nucleo-albumin."* This ring is

easily distinguished by its location from that due to serum albumin; it is, itself, at present, of no clinical significance.

Experience soon enables a careful worker to avoid errors arising from these sources. Heller's test is widely used. Heller's test and the heat and acetic acid test are sufficient for clinical purposes; it is wise to become thoroughly conversant with the interpretation of these two tests rather than to use more.

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iii. Quantitative Determination of Albumin

1. *Estimation of the Volume of the Precipitate in the Heat and Acetic Acid Test*

If the precipitate in the heat and acetic acid test be allowed to settle and the volume estimated at the end of an hour, an *approximate* conclusion regarding the percentage of protein in the urine can be reached.

(a) 2–3 per cent of albumin = whole fluid a compact coagulum.
(b) 1 per cent of albumin = the precipitate is a little more than half the volume of the urine.
(c) 0.5 per cent of albumin = precipitate ⅓ of volume.
(d) 0.25 per cent of albumin = ¼ of the volume.
(e) 0.1 per cent = 1/10 of the volume.
(f) 0.05 per cent = just a little at the bottom of the tube.
(g) Less than 0.01 per cent = only a turbidity, no precipitate.

2. *Tsuchiya's Modification of the Esbach Method*

In this test the Esbach albuminometer tube is used with a new reagent, devised by Tsuchiya, for precipitating the coagulable protein. The formula of this reagent is:

Phosphotungstic acid	1.5 gm.
Hydrochloric acid, conc	5.0 c.c.
Alcohol, 96 per cent, to	100.0 c.c.

Technic.—If the urine is alkaline, it is first acidified with acetic acid. The Esbach tube is filled with the acid urine to the mark U, and then the reagent

is added to the mark *R*. The tube is now corked with the rubber stopper and inverted (not shaken) twelve times in order to thoroughly mix the contents. It is then left in a vertical position for 24 hours at room temperature; after which the amount of albumin is read off, the graduations on the tube representing the number of grams of albumin *per liter* of urine.

Fig. 435.—Esbach's Albuminometer; on Glass Foot. Graduated to Read Grams of Albumin per Liter of Urine. (By courtesy of A. H. Thomas Co., Phila.)

Tsuchiya's reagent is a great improvement over the reagent advocated by Esbach, which gave wholly unreliable results. The average error with Tsuchiya's reagent is said by Morris to amount to less than 0.3 gram per liter (controlled by the Kjeldahl and gravimetric methods). Tsuchiya's method is recommended for clinical use.

3. Scherer's Method

For more accurate studies, the following method must be used.

A few drops of acetic acid are added to 50–100 c.c. of filtered urine. Boil. After cooling, the precipitate is collected on a dried and weighed filter, washed with alcohol and ether, dried at 100° C., weighed, and the weight of the filter subtracted from the total weight. The filtrate must be transparent and free from protein. If desired, the precipitate, along with the filter, can be washed and the nitrogen content estimated by Kjeldahl's method. If the N-value be multiplied by 6.25 the weight of the protein in grams is obtained (approximately).

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iv. Removal of Albumin from the Urine

It is frequently necessary to remove albumin from the urine as the presence of this body interferes with certain tests. This is usually done by acidifying with acetic acid and boiling. The flocculent precipitate is removed by filtration. The clear filtrate is tested by one of the other tests to determine whether it is albumin free. In some studies, it may be desirable to use the newer methods of deproteinizing fluids, say with dialyzed iron or with kaolin (see Methods of Removal of Proteins from Blood, Part VII).

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(*b*) *Nucleo-albumin; Mucin; Mucoid*

Confusion exists as to the nature of the substances to which the above terms have been applied. On adding acetic acid to diluted urine, a faint clouding will usually be observed in the cold. The substance thus precipitated is usually called *"nucleo-albumin."* "Nucleo-albumin" is a term applied to certain compound proteins that contain phosphorus in some combination other than the prosthetic group, nucleic acid. The above precipitate probably has much closer affinity with the mucins. The *mucins* are glycoproteids, *i. e.,* compound proteins containing a carbohydrate-radicle, glucosamin. The mucins are proteids of an acid character, contain no phosphorus, but are rich in sulphur, which in certain of them is in the form of chondroitin-sulphuric acid. Mörner states that the precipitate in a normal urine, after the addition of acetic acid in the cold, is formed of the normal trace of serum albumin combined with certain acid, sulphur-containing, substances, especially chondroitin-sulphuric acid, taurocholic acid and nucleic acid, the combined bodies being precipitated in the presence of acetic acid. The clinical significance of the precipitate is, at present, chiefly due to the possibility of its being mistaken for serum albumin in the tests for serum albumin.

Aside from this, as yet not definitely classified, "mucinlike" body that has just been described, the urine usually contains a *true mucin* or *mucoid,* which, on standing, goes out of solution to form the *nubecula,* the filmy strands of which are to be observed in most normal urines. This substance is also precipitated in the cold by acetic acid, but redissolves in excess of the acid. It contains a reducing body, but no phosphorus; sulphur containing acids, of which chondroitin-sulphuric acid is the commonest, are also present in it. It is increased in inflammatory conditions of the genito-urinary tract, especially in cystitis.

Both this true urinary mucin, and the mucinlike substance to which the name nucleo-albumin has been wrongly given, are therefore compound proteins; and they yield the characteristic protein color and precipitation reactions.

A certain importance attaches to the fact that these substances are present in the urine in *colloidal solution;* in fact, they are the chief colloids in normal urine. To their *protective action* is due the lack of precipitation of salts that are frequently present in the urine in supersaturated solution.

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(*c*) *Bence-Jones Protein* (*Myelopathic Albumosuria*)

This substance is apparently an instance of the formation in the body in disease, of a protein of distinctly abnormal character. It is apparently a true protein, with the typical amino-acid grouping, and its molecule is larger than that of any albumose. The physicochemical properties and

the chemical composition of the protein distinguish it, however, from other proteins. These reactions cannot be gone into, in detail, here. In chemical composition, it is characterized by a high aromatic-radicle content. The most striking physicochemical properties are given by Wells as follows:

"The coagulation temperature is low, varying from 49°–60° C. in various cases and being considerably modified by the amounts of salt and urea present in the solution.

In many cases the coagulum is redissolved on heating and reappears on cooling, but this characteristic feature is not always present and often disappears in cases where at first it is present.

A precipitate is formed by strong (25 per cent) nitric acid, which disappears on heating and reappears on cooling. Strong hydrochloric acid produces a dense precipitate that is quite typical (Bradshaw).

No precipitate is produced by acetic acid even in excess and the addition of acetic acid to a hot coagulated specimen causes prompt solution of the coagulum.

Unlike albumose, this substance does not dialyze; the salt free solution left in the dialyzing bag does not precipitate.

A purplish violet color is usually given with the biuret-reaction, but it may be more reddish in color, especially if little copper be present.

Sulphur is readily split off by alkalis, reacting with lead acetate to produce lead sulphid (Boston).

After standing in alcohol, by which the body is precipitated, it loses its solubility (differing in this respect from albumose)."

The excretion of Bence-Jones protein has been observed in many cases of *multiple myeloma* and in a few cases of leukemia, chloroma and carcinoma with bone metastases. A few cases of multiple myeloma have been described without the proteinuria. In cases in which this substance is excreted it tends to show rather constant properties.

In the body, the protein has been found only in the myeloma tissue; it is not found in the other organs, or tissues, of patients with multiple myeloma; nor is it found in normal bone marrow. The amount excreted does not vary with the diet; and it is therefore probable that the protein is formed from constituents of endogenous origin. As much as 30 to 70 grams a day of the protein may be excreted. This large output makes it seem probable that the protein is produced as a result of some change in the general protein metabolism caused by the tumor or its products, rather than that the protein is produced directly by the tumor tissue itself.

Tests for Bence-Jones Protein.—The most important differential characteristic of this protein is its coagulation at a temperature of 45° to 60° C. with solution of the coagulum at boiling temperature and reprecipitation on cooling. Slow heating, in a water bath containing a thermometer, is an easy method of determining the coagulation-temperature. A confirmatory test is made by adding a few drops of 25 per cent nitric acid to another specimen of the urine, when a precipitation will occur in the cold that will increase at 60° C., and the precipitate will again

undergo solution at 100° C. A precipitation should likewise occur when two volumes of saturated ammonium sulphate are added to another specimen of the urine. These tests suffice for identification of the protein (Boggs and Guthrie).

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(*d*) *Hemoglobin and Its Derivatives* (*Including Bile Pigments*)

Under this caption the excretion of the chromoproteid *hemoglobin*, will first be dealt with. The subject of the elimination of the non-protein pigments derived from hemoglobin will then be discussed. These are divisible into the pigments such as *hematin* and *hematoporphyrin* that are directly derived from the chromogen group of hemoglobin; and the *bile pigments* whose relationship to hemoglobin is less direct.

i. Hemoglobin in the Urine (Hemoglobinuria)

The chromoproteid, hemoglobin, may be found in the urine either in free solution (*hemoglobinuria*), or as a constituent of the stroma of red blood corpuscles present in the urine (*hematuria*). It is true that, in all cases of hematuria some *laking* of the red blood corpuscles takes place, with solution of hemoglobin in the urine; but it is advisable to reserve the term *hemoglobinuria* strictly for those cases in which, as a result of hemoglobinemia, the kidney excretes the protein, hemoglobin. The reason lies in the sharp clinical distinction between the two conditions.

Hematuria, the elimination of red blood corpuscles in the urine, is usually due to pathological conditions affecting the genito-urinary tract. Thus it is met with in acute forms, or stages, of nephritis, in infarcts of

the kidney, in renal, ureteral, or vesical stone or tumor and in hemorrhagic cystitis, etc. An idiopathic or essential hematuria also occurs (*vide* Microscopic Examination of the Urine). Hematuria is detected by the finding of red blood corpuscles on microscopic examination of the urinary sediment.

Hemoglobinuria is dependent upon the occurrence of hemoglobinemia. Red blood corpuscles are constantly disintegrating in the blood, but this is normally insufficient in amount to lead to hemoglobinemia. It is only when the amount of hemoglobin set free in the blood stream exceeds the capacity of the liver to convert it into bilirubin that an accumulation of hemoglobin in the blood takes place with consequent hemoglobinuria. It is estimated that one-sixtieth of the hemoglobin of the body must be set free from red blood cells before hemoglobinuria occurs (Webster).

Hemolytic *poisons* are the chief etiological factors in the production of hemoglobinuria. Such are snake venom, chlorates, carbolic acid, carbon-monoxid, chloroform, pyrogallic acid, etc. After *blood transfusions,* severe *burns,* and in the course of *severe cases of certain infectious diseases,* sufficient intravascular hemolysis occurs to lead to hemoglobinuria.

There is also a so-called "*paroxysmal type of hemoglobinuria*" (see Part VII), which is not uncommon in congenital lues.

The *color* of the urine in hemoglobinuria is usually distinctly red (oxyhemoglobin), or dark reddish brown (methemoglobin). Methemoglobin is more constantly present than oxyhemoglobin. A mixture of both is usual. In hematuria, the color is much the same but the urine is more likely to be hazy, or smoky, instead of clear.

The urine in hemoglobinuria will of course give the usual protein tests with heat and acetic acid, etc., but to identify the protein the prosthetic chromogen group must be shown to be present. With the presence of hemoglobin proven it is next necessary to determine by a careful microscopic examination of a *fresh specimen* whether red blood corpuscles are present or not.

Two types of tests for hemoglobin are much used in this connection. The first type, which includes the guaiac, aloin, and the benzidene tests, is not entirely specific for hemoglobin, since other substances may give a positive reaction. On the other hand these tests are very delicate so that a negative reaction is of marked significance. The spectroscopic tests on the other hand are specific but a spectroscope is not always available. The hemin-crystal test is likewise specific when obtained, but a negative result is not conclusive. A combination of the guaiac test and of the spectroscopic test is suitable for clinical use.

1. Guaiac Test for Hemoglobin

Technic.—About 25 c.c. of urine are acidified with 5 c.c. of glacial acetic acid. The mixture is then extracted with 20 c.c. of ether. The ether is poured off. A portion of this ether extract is then layered in a test tube upon a mixture of

equal parts of a fresh alcoholic solution of guaiac resin and of hydrogen peroxid. If hemoglobin is present a distinct blue color will develop at the line of junction of the two solutions and will extend into the ether layer. This color may develop only after standing for a minute or more and persists only a short time.

It is important for this test that the glassware be carefully cleaned. It is well to rinse the test tubes to be used with alcohol. Tubes that have contained copper solutions (Fehling's) frequently give a blue color with guaiac.

If the test is positive it should be confirmed by spectroscopic examination of the remainder of the ether extract (*vide infra*) since a positive test is not absolutely specific for hemoglobin. It is well from time to time to test the efficiency of the reagents by a control examination of a dilute solution of blood. A negative result obtained with tested reagents may be taken as proof of the absence of hemoglobin.

2. *Spectroscopic Test for Hemoglobin*

Technic.—A portion of the ether extract left from the preceding test is best used for the spectroscopic examination. The spectrum of acid hematin is looked for. According to Schumm it is well to add to this ether extract ammonia in excess (keeping the mixture cool), and, after shaking well, to pour off the ammonia layer and a portion of the ether into a glass. Ammonium sulphid is then added and the mixture examined spectroscopically. The bands of alkaline hemachromogen are then looked for. (For details of spectroscopic examination consult Examination of the Blood, Part VII.)

3. *Teichmann's Hemin-Crystal Test*

Technic.—A solution of tannic acid is added to the urine and the precipitate collected upon a filter paper and washed with very dilute acetic acid. The precipitate is then dried on the filter paper and a small amount of it transferred to a clean glass slide. A *small* amount of powdered sodium chlorid is mixed on the slide with the precipitate. A cover glass is placed over the mixture, and glacial acetic acid is run under it. The preparation is then heated to the steaming point for 1 minute, replenishing the acid if necessary. The specimen is allowed to cool and is then examined microscopically for the brown rhombic plates of hemin. High magnification may be required. It is often necessary to reheat the specimen several times.

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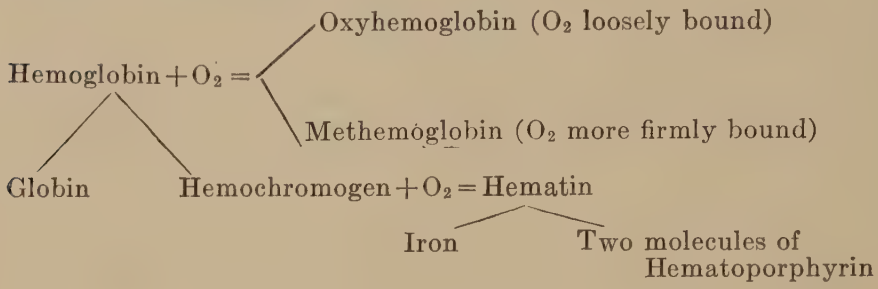
ii. Non-protein Blood Pigments Derived from Hemoglobin

The relation of hemoglobin to these compounds and derivatives is illustrated in the following table:



1. Hematoporphyrin

Hematoporphyrin, a reduced iron free hematin, is found in the urine after long use of sulfonal, trional and tetronal, and sometimes in typhoid fever and other conditions. In minute traces it may be present in normal urine. With W. L. Estes, Jr., I have described a form of family hematoporphyrinuria associated with chronic dilatation of the duodenum and stomach. When this pigment is present in the urine the fluid is almost opaque in direct light and looks black. In thinner layers it is a brownish red or port wine color. Even pale urine may contain hematoporphyrin or its chromogen. Boiling does not change the port wine color. The urine may be free from albumin in such cases.

Test for Hematoporphyrin in the Urine.—To 100 c.c. of urine add 20 c.c. of 10 per cent NaOH solution. This precipitates the phosphates, which carry down the hematoporphyrin with them. Collect the precipitate on a small filter, wash first with a little distilled water, then with 96 per cent alcohol. The precipitate is then dissolved by pouring on the filter from 2–5 c.c. of alcohol containing 1 drop of HCl per cubic centimeter. The alcoholic solution will yield the spectrum of acid hematoporphyrin (a band in the yellow and one in the green), or on the addition of ammonia and filtering again four bands appear (alkaline hematoporphyrin), one in the red, one in the yellow, one in the green and one in the blue (*vide* spectral analysis of blood).

2. Hematin

According to Neuberg, this pigment is not infrequently present in pathological urines but is overlooked or its spectrum confused with that of methemoglobin.

Test for Hematin.—This pigment yields four bands (in both acid and neutral solutions): one between C and D, the three others feebler, in the yellow, green and blue. If the solution be made alkaline the violet end of the spectrum is darkened and a band appears to the left of D. On adding ammonium sulphid, reduced hematin (hemochromogen) is formed; the band near D disappears and in its place two broad bands between D and E and near E appear.

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iii. Bile Pigments in the Urine (Choluria and Urobilinuria)

The excretion of bile pigments is discussed at this point because of their close chemical and physiological relationship to the blood pigments.

The clinical significance of these pigments is obvious after a brief survey of their origin. Hemoglobin derived from the disintegration of red blood corpuscles is carried to the liver. The chromogen group there yields, by intermediary steps that are not fully known, the bile pigment bilirubin. Bilirubin passes into the intestines, where as a result of bacterial action it is reduced to urobilin. Urobilinogen constitutes a stage in this process. Urobilinogen and urobilin are reabsorbed into the blood. A portion of each is excreted by the kidney. The remainder is changed in the liver back into bilirubin. Hence there is normally an excretion of urobilinogen and urobilin in the urine, but not of bilirubin.

When there is excessive blood destruction as in certain fevers, hemorrhagic extravasations, hemolytic poisoning, etc., there is a great increase in bilirubin formation, and consequently of urobilin production in the intestines. The urobilin absorbed is greater in amount, and urobilin and

urobilinogen are increased in the urine. The urine may become a deep yellowish brown color. The change of the colorless urobilinogen to urobilin under the action of light probably explains the deepening of color that appears on standing.

Beyond a certain point blood destruction results in an icteric tinge of the skin and the appearance of bilirubin in the urine. The explanation most generally accepted of this phenomenon is that the abnormal increase in bilirubin formation in the liver (because of the excess of hemoglobin brought there) so increases the viscosity of the bile that biliary passages of capillary size are blocked and, from these, absorption of bilirubin into the blood occurs with resultant jaundice and bilirubinuria. At the same time the bile rich in bilirubin that does reach the intestines is sufficient to cause the usual increase in urobilin that accompanies less marked blood destruction.

In catarrhal jaundice, in gall-stones, in hepatic cirrhosis, etc., a similar obstruction of the bile secretion occurs with resorption of bilirubin, jaundice and bilirubinuria. When there is complete obstruction of the common duct, due to carcinoma of the head of the pancreas, stenosis of inflammatory origin, etc., no transformation of bilirubin to urobilin can occur and as a consequence no urobilin is found in the urine. At the same time the bile stasis in the liver leads to absorption of bilirubin into the blood with resulting icterus and bilirubinuria.

From these facts it is evident that the determination of the presence of urobilin in the urine is of no clinical importance. Quantitative determinations would be of interest; but the quantitative methods are not feasible for clinical use. On the other hand, the determination of the absence of urobilin furnishes valuable information as to the occlusion of the common duct. Qualitative tests for bilirubin in the urine give important confirmatory evidence of the presence of icterus.

1. Bilirubin and Its Oxidation Products

In the fresh urine, bilirubin is usually present alone, but, on standing, this pigment is oxidized, giving rise to a series of derived pigments, biliverdin, bilicyanin, bilifuscin, biliprasin, cholecyanin, and choletelin. Such a urine shows, accordingly, various shadings of color—greenish yellow, yellowish brown, greenish brown, etc. The fresh specimen containing bile pigment has usually a brownish color like beer.

The Foam Test.—When urine containing bile pigments is vigorously shaken, the foam presents a distinct yellow color. Urine in other conditions may be of a tinge resembling that of the urine in jaundice, but the yellow foam is specific for the presence of bile pigments. Only a distinct yellow color can be taken as a positive test, however, and this shade is given only when considerable amounts of bile pigment are present.

Trousseau's Test.—A 1 per cent alcoholic solution of iodin is layered upon a few c.c. of urine (acidified if necessary with acetic acid). If bilirubin be present an emerald green color is observed at the point of contact. Antipyrin or thymol may lead to the formation of a similar color. The test indicates one part of biliary pigment in 10,000 of urine.

Gmelin's Test.—To a few c.c. of conc. nitric acid in a test tube a small chip of soft wood is added. When the acid assumes a faint yellow tinge, due to formation of nitrous acid, it is poured into another test tube, and on it is carefully layered the acidified urine. A play of colors is observed at the line of contact of the two fluids—green, blue, violet, red and yellow from above downward. Of these the green color is the most characteristic. An excess of indican may vitiate the test by leading to the presence of a deep blue ring. The reaction is said to indicate one part of bilirubin in 80,000 of urine.

In *Rosenbach's modification* of Gmelin's test, the urine is filtered several times through the same filter; this filter is then spread out on a porcelain plate and touched with a few drops of the nitric acid mixture. The characteristic colors appear in rings around each drop of nitric acid. Brownish stains often appear with normal urines; unless the characteristic green is present the test should be called negative.

2. Urobilin

Since the clinical importance of urobilin determinations is associated with the obtaining of a negative test, it is wise to take the following preliminary measures to increase the significance of the result:

Preliminary Extraction.—About 100 c.c. of urine are acidified with hydrochloric acid. Four c.c. of Lugol's solution are now added to convert any urobilinogen present to urobilin; and the mixture is then extracted with 10 c.c. of amyl alcohol. The amyl alcohol extract is then used for the following tests:

Schlesinger's Test.—If an amyl alcohol extract is not used 10 c.c. of urine are treated with 3 to 5 drops of Lugol's solution. The 10 c.c. of urine, or 5 c.c. of the amyl alcohol extract (*vide supra*), are then added to an equal amount of Schlesinger's reagent (10 grams zinc acetate in 100 c.c. of absolute alcohol; the solution is turbid and should be shaken well and filtered before using). The mixture is filtered. The test tube containing the filtrate is held against a dark background; if urobilin be present a beautiful green fluorescence will be visible. The fluorescence may be brought out more distinctly if the light be focussed on the tube with a small hand lens.

When bilirubin is present in large amounts, it should be precipitated by the addition of 2 c.c. of 10 per cent calcium chlorid solution to 8 c.c. of urine. This mixture is filtered and the test applied to the filtrate. The test is said to be sensitive to 0.002 per cent dilution of urobilin.

Spectroscopic Determination of Urobilin.—In the presence of a considerable excess of urobilin the urine may be examined directly with the spectroscope. Usually it is best to use a portion of the amyl alcohol extract (*vide supra*). The spectrum of acid urobilin is looked for. It shows an absorption band to the right of E, the left border of which reaches nearly to b, while the right border encloses F.

5. *Urobilinogen*

Urobilinogen is normally present in the urine when voided. Within a few hours it is converted to urobilin. Its absence in freshly voided urine is confirmatory of a negative test for urobilin.

Test for Urobilinogen; Ehrlich's "Aldehyd Reaction."—To 10 c.c. of urine add a few drops of a 2 per cent solution of p-dimethylaminobenzaldehyd in 20 per cent HCl. If much urobilinogen be present the fluid will at once turn red. In normal urine the amounts are so small that the red color appears only on heating. If no red color appear on boiling urobilinogen is entirely absent (complete obstruction to ductus choledochus; severe diarrheas).

The test is unreliable in any but perfectly fresh urines and in the presence of excess of indol or of skatol. A similar reagent has been used by Neubauer and Rohde as a test for tryptophan. Ehrlich's aldehyd reaction is also said to be positive with histidin.

4. *Biliary Acids in the Urine*

Though these are wholly different, chemically, from biliary pigments, their presence in the urine in jaundice makes it convenient to mention them here. Their demonstration clinically is difficult and without diagnostic importance. Pettenkofer's test may be applied as follows:

A few grains of granulated sugar are added to a little urine placed on the cover of a porcelain crucible, along with a few drops of concentrated H_2SO_4; evaporate, with gentle heat, to dryness; if biliary acids be present a purple color appears due to furfurol. Since similar reactions can be yielded by other substances (protein, fatty acids, etc.), the test to be reliable should be made upon the biliary acids after isolating them from the urine. This procedure is, however, complicated, consisting of evaporating to dryness, extracting with alcohol, precipitating with lead salts or baryta, and extracting the precipitate with alcohol or hot water. (See large text-books.)

Melanin

In cases of melanotic tumors and in some cases of chronic malaria the urine may contain a chromogen (melanogen) that is converted on exposure to air into the dark pigment melanin. This coloration may be intensified by the addition of ferric chlorid solution, a reaction that helps to differentiate this chromogen from indican. Thormahlen found that melanogen-containing urine gives a violet color with sodium nitroprussid and NaOH; upon addition of acetic acid this violet changes to a beautiful blue.

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3. Non-coagulable Derivatives of Protein Yielding a Biuret Reaction (Peptones; Albumoses)

(*a*) *Albumose in the Urine* (*Albumosuria*)

The ill-defined group of proteoses that, in protein hydrolysis, stand in the intermediary position between the acid-albumins and the peptones, is represented in the urine by the occasional appearance of "albumoses" chiefly the so-called *deutero-albumose.* The appearance of these intermediary bodies is apparently a sequence of their accumulation in the blood. This accumulation may be due to their absorption from the bowel since *albumosuria* is common in ulcerative conditions of the intestine; but in many instances it is apparently a consequence of pathological increase in protein catabolism. Thus albumosuria is found during the *autolysis* of purulent exudates, in leukemia, carcinoma, the puerperium, and in all febrile disorders. In many of these cases it is of course associated with albuminuria.

i. Tests for Albumose in the Urine

The following methods will enable the clinician to feel reasonably sure of the presence of albumose:

Bang's Test.—In a test tube 10 c.c. of urine are shaken with 8 grams of powdered ammonium sulphate, and heated until the salt is dissolved. The mixture is boiled a few seconds and then centrifugalized for one-half to one minute

to throw down the precipitate. The supernatant fluid is decanted and the precipitate extracted with alcohol to remove urobilin. The alcohol is poured off and the residue is then brought into solution in a small amount of water. This solution is boiled and filtered to remove albumin and the filtrate is shaken out with chloroform to remove any remaining traces of urobilin. After separation from the chloroform the watery solution is treated first with a few drops of strong sodium hydrate and then with a few drops of dilute (2 per cent) copper sulphate solution. On warming this mixture a beautiful red violet color will be observed (biuret test).

Fittipaldi's Test.—To 10 c.c. of urine 60 c.c. of alcohol are added and the mixture is allowed to stand till the next day. The fluid is then carefully decanted from the precipitate; and the latter is dissolved in the least possible amount of 30 per cent NaOH, and this alkaline solution is treated with a few drops of freshly prepared ammoniacal nickel solution (5 per cent solution of nickel sulphate plus an equal volume of ammonia water). The presence of albumose or peptone is shown by an orange red coloration.

(*b*) *Peptone in the Urine* (*Peptonuria*)

Peptone has never definitely been proven present in the urine; though many reports of peptonuria are to be found in the literature.

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4. A-biuret Protein Derivatives in the Urine

(*a*) *Amino-acids in the Urine* (*Amino Aciduria*)

i. Significance of Amino Aciduria

The amino-acids occur in the body as a stage in both the anabolism and catabolism of tissue protein. It is logical, therefore, to expect to find them present, though in small amounts, in the normal blood and urine; and this has been shown to be the case (Van Slyke, L'Abbé, Bith, etc.). Van Slyke has shown experimentally that absorbed amino-acids from the diet are quickly removed in great part from the blood stream apparently by adsorption of the amino-acids by the tissues. In the tissues the amino-acids may be demonstrated for some time; their disappearance being coincident with a rise in the urea content of the blood. The disappearance of amino-acids from the blood is not complete. In dogs, 3-8 mg. of amino-acid-nitrogen per 100 c.c. of blood are found even after long hunger periods. Hence amino-acids are apparently proven to be a stage in the disintegration of tissue protein. Abel by his ingenious method of dialyzing the blood in the living animal has shown the presence of relatively large quantities of free amino-acids in normal blood. The clinical findings harmonize with this conception.

The amino-acid nitrogen in the normal total 24 hours urine as determined by Sörenson's method varies between 0.236 g. and 1.06 g., which constitutes 1.58–4.35 per cent of the total nitrogen.

The cases of pathological increase in the amino-acid nitrogen fraction in the urine are divisible into those in which there is a defect in protein metabolism that affects the excretion of *all* the amino-acids and those in which a defect in the utilization of a *single* amino-acid results in its excretion in large quantities (*vide* Amino-acid Diatheses, Part XIII).

Cases of increase of the amino-acids in general in the urine may be due to defective utilization of amino-acids, as in certain hepatic diseases; or they may be due to a pathological increase in amino-acid formation as in extensive tissue destruction; and, finally, they are apparently sometimes a result of defective protein metabolism in diabetic acidosis (Cammidge). It is probable that the active investigation of these phenomena will in the near future give to amino-acid determinations a more definite clinical value than they now possess.

ii. Determination of Total Amino-acids in the Urine

The total amino-acid content of the urine is usually expressed in terms of the amino-nitrogen content as determined by formalin titration. The determination of the presence of single amino-acids is, on the other hand, a very much more difficult matter. Leucin, tyrosin, and glutamin, are readily isolated by taking advantage of their peculiarities of solubility. Certain other amino-acids can be separated by precipitation. For the greater portion of the amino-acid bodies, resort must be had to Emil Fischer's esterification method. The mixture of amino-acids is esterified with alcohol and hydrochloric acid. The various esters are then obtained separately by means of fractional distillation.

The Formalin-Titration Method (Sörensen-Henriques)

Principle.—This method depends upon the union of formalin with the amino group of the amino-acids. The amino group thus loses its basic properties. The amino-acid then loses its amphoteric character and becomes a true acid, which is determined by titration.

$$\mathrm{R.\underset{\displaystyle COOH}{\underset{|}{CH}}.NH_2 + CH_2O = R.\underset{\displaystyle COOH}{\underset{|}{CH}}.N{:}CH_2 + H_2O}$$

Since ammonia is likewise determined in the urine by formalin titration, the figures obtained by this titration represent the sum of amino-acid nitrogen and ammonia nitrogen. Ammonia is determined separately

by Folin's method, and the ammonia nitrogen, thus determined, is subtracted from the formalin titration results; the remainder is the amino-acid nitrogen.

Technic.—Fifty c.c. of urine are pipetted into a 100 c.c. graduated flask. One c.c. of phenolphthalein solution (0.5 gm. phenolphthalein dissolved in 50 c.c. alcohol plus 50 c.c. water), and 2 gm. of solid barium chlorid are now added. The mixture is shaken until the barium chlorid is dissolved. A saturated solution of barium hydroxid is then run in until the solution assumes a red color, after which 5 c.c. excess are added. The mixture is now made up to 100 c.c. with water. After thorough shaking followed by standing for 15 minutes the mixture is filtered through a dry filter.

Eighty c.c. of the clear red filtrate (i. e., 40 c.c. of urine) are pipetted into a 100 c.c. graduated flask, and neutralized to sensitive litmus paper by the addition of N/5-hydrochloric acid. Freshly boiled water is then added to the 100 c.c. mark.

Two portions of 40 c.c. each (16 c.c. of urine) are then taken. In one the ammonia is determined by Folin's method. In the second, the formalin titrable nitrogen is determined as follows:

To 50 c.c. of commercial formalin is added 1 c.c. of phenolphthalein solution (*vide supra*) and sufficient N/5-NaOH to bring the color to a faint rose.

Forty c.c. of freshly boiled, distilled water plus 10 c.c. of the neutralized formalin plus 5 c.c. of N/5-NaOH are titrated with N/5-HCl. The acid is added with constant shaking until the fluid is of a pale rose color; then one drop more of N/5-NaOH is added, which brings out a distinct red color; and finally another two drops, which makes the color strong red. This color is to serve as a standard to which the urine in turn must be titrated.

To 40 c.c. of the neutralized urine mixture (*vide supra*) are added 10 c.c. of the formalin mixture and N/5-NaOH to about 2 c.c. past the neutral point. The mixture is titrated back with N/5-HCl until the color of the solution is paler than that of the control solution. N/5-NaOH is now again added until the color just matches that of the standard.

The number of c.c. of N/5-NaOH used in this last titration, minus the number of c.c. of N/5-HCl used in titrating back, and minus the number of c.c. of N/5-NaOH needed to neutralize the acidity of the formalin (as determined from the control titration), is a measure of the united ammonia and amino-acid nitrogen. If this number of c.c. be multiplied by 2.8 the result is the grams of nitrogen attributable to ammonia and amino-acids in the amount of urine used (16 c.c.). The ammonia nitrogen in grams as determined by Folin's method is now subtracted and the remainder is the amino-acid nitrogen in grams for 16 c.c. of urine.

2. *Determination of Free Amino Nitrogen in the Urine (Van Slyke)*

After hydrolysis with sulphuric acid and removal of the ammonia the free amino nitrogen in the urine is determined with Van Slyke's apparatus. Nitrous acid added to the urine reacts with the free amino groups yielding free nitrogen quantitatively. When the apparatus is available this method is preferable to the formalin titration method.

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iii. Determination of Leucin and Tyrosin in the Urine

Leucin and tyrosin because of their tendency to be precipitated in crystalline form were early found in the urine. Frerichs linked their presence with the occurrence of acute yellow atrophy of the liver and while it is now known that they are present in the urine in many other conditions it remains true that they are more constant and far more abundant in acute yellow atrophy (as high as 1.5 gm. of tyrosin a day has been found). They are commonly present also in the urine in phosphorus poisoning. The presence of leucin and tyrosin is usually associated with that of other less easily recognized amino-acids. In experimental phosphorus poisoning, leucin, tyrosin, glycocoll, and phenylalanin have been recovered from the urine (Abderhalden and Barker).

Test for Leucin.—The impure crystals of leucin found in the urine are yellowish refractile spherules with concentric layers, alternately light and dark. They are radially striated. When the crystals are not present but leucin is suspected, the urine should be evaporated to a small bulk and alcohol added. This procedure favors their precipitation.

Scherer advises that the urine be evaporated to semisolid consistency and some of the residue mixed with concentrated nitric acid be re-evaporated on a plat-

inum crucible lid. The residue is heated with a few drops of sodium-hydrate solution, which will give it a brownish color and cause it eventually to collect into an oily drop that rolls about on the heated surface. Methods for more complete identification must be sought in larger hand-books.

Test for Tyrosin.—The crystals of tyrosin in the urine are fine colorless needles arranged in sheafs and rosettes. If the crystals are not characteristic *Mörner's test* is applied. The urine is evaporated to a semisolid state and the residue dissolved in a small amount of water. One c.c. of Mörner's reagent (1 c.c. formalin in 55 c.c. conc. sulphuric acid and 45 c.c. of water) is added to the aqueous solution and the mixture heated to boiling. The presence of tyrosin gives a fine green color. The methods for complete identification of tyrosin are to be found in larger hand-books.

iv. Alkaptonuria

This condition is characterized by the voiding of urine that turns dark on exposure to air due to its content of *homogentisic acid.* This substance is derived from *tyrosin* and *phenylalanin,* and is excreted because of the inability of the body to split open the benzin ring it contains. A metabolic defect is therefore present, which affects the catabolism of only those two amino-acids that contain the benzin ring (*vide* Alkaptonuria, Amino-acid Diathesis, Part XIII).

Tests for Homogentisic Acid

The presence of homogentisic and uroleucic acids will be suspected clinically when the urine on standing turns reddish brown or black, or when it is found strongly to reduce copper solutions. If the characteristic color is not present it may be brought out by adding ammonia to the urine and agitating it from time to time during a period of 12-24 hours. The reducing power of homogentisic acid may lead to its confusion with d-glucose, but homogentisic acid does not reduce bismuth, does not yield the phenylhydrazin reaction and is non-fermentable and optically inactive. Homogentisic acid reduces ammoniacal silver solution in the cold.

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v. Cystin in the Urine

(For a discussion of the appearance of cystin in the urine the reader is referred to Part XIII, Amino-acid Diatheses).

Test for Cystin.—When cystin is suspected in the urine an attempt should be made to obtain the cystin crystals. In rare cases these occur spontaneously. Their precipitation is favored by acidifying a large specimen of the urine and allowing it to stand for 12–48 hours in the ice chest. Two forms of crystals occur: "(1) six-sided tablets having an opalescent luster and sometimes traced with fine lines of secondary crystallization; (2) four-sided square prisms lying separately or in stellate forms" (Webster). Hydrochloric acid and alkaline hydrates dissolve cystin crystals; but acetic acid leaves them undissolved. These tests differentiate cystin crystals from those of uric acid. Urine containing cystin gives a large precipitate of benzoyl cystin when treated with strong sodium hydrate solution and a few drops of benzoyl chlorid. Methods for more complete identification will be found in larger text-books.

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5. Carbohydrates (Sugars) in the Urine

A variety of carbohydrates (sugars) have been demonstrated in human urine in pathological conditions. The general term *melituria* has been suggested by Naunyn as applicable in all these instances. The most

important one of these is the occurrence of ordinary d-glucose (dextrose) in the urine; a condition that is called glycosuria. Similarly, but less frequently, there are encountered cases of levulosuria, lactosuria, galactosuria, maltosuria and pentosuria. There are also cases of *mixed melituria* in which two sugars are excreted simultaneously.

It is essential for an understanding of these conditions that the chemical relationships of the carbohydrates, and the essential points in carbohydrate metabolism should be kept in mind. The reader is referred to the discussion of Carbohydrate Metabolism in Part XIII.

(*a*) *d-Glucose in the Urine* (*Glycosuria*)

i. Sources, Distribution and Excretion of d-Glucose

The *normal urine* contains a trace of d-glucose but not sufficient to affect our usual qualitative tests. The total reducing substance in normal urine of adults averages 0.21 to 0.24 per cent, of which glucose constitutes but 18 per cent (Bang and Bohmannson).

Carbohydrates taken in as *food* in the form of starches, sugars, etc., normally undergo cleavage in the digestive tract to monosaccharides and are *absorbed* in this form, undergoing change to d-glucose in the intestinal wall. In addition to the sugar arising directly out of the food the body builds a certain amount of sugar out of the nitrogen free residues of the amino-acids derived from the digestion of *protein*. Possibly sugar may also be formed in the body from *fat*. The endogenously formed sugar of the body is *d-glucose*.

The normal content of the systemic *blood* in d-glucose is about 1 part in 1,000 (0.1 per cent). If the sugar attains a concentration in the blood of over 0.2 per cent (*hyperglycemia*), the kidney actively secretes sugar (*glycosuria*). The occurrence of glycosuria is usually avoided by means of various methods the body possesses of *storing* the sugar derived from exogenous and endogenous sources.

The most important of these storage methods lies in the polymerization of sugar to form *glycogen*, which is deposited in the liver and in the muscle tissue. These glycogen deposits serve in turn as a source of sugar when need arises.

There is also evidence in favor of the *adsorption* of glucose by the colloids of the blood and tissues. The formation of such combinations would serve to remove excess sugar from the blood and prevent hyperglycemia due to free sugar.

The formation of *fat* from sugar may also be looked upon as a method for the disposal of excess sugar.

Aside from these storage mechanisms, sugar is, normally, constantly

being utilized in the body as a source of energy by means of its *oxidation* to CO_2 and H_2O.

ii. Types of Glycosuria

It is of interest to indicate briefly the *types of glycosuria* that are explainable by derangement in some one of the above factors that regulate carbohydrate physiology. A further discussion of the subject will be found in Part XIII, see Diabetes.

Alimentary Glycosuria. — This appears when the normal person exceeds the glucose intake that can be disposed of in the normal body by utilization or storage without hyperglycemia resulting. An intake of over 100 gms. of glucose is necessary to produce glycosuria in the normal adult.

Glycosuria from Excessive Glycogenolysis.—A large series of glycosurias result from conditions that cause a rapid formation of sugar from the stored up glycogen.

The best known of these is the *piqûre* of Claude Bernard, a puncture of the floor of the fourth ventricle (glycogenic center), which leads to a rapid reduction of glycogen in the liver, to hyperglycemia and to glycosuria. The maintenance of stored glycogen in the liver is apparently dependent upon nervous control; and an efferent and afferent path have been traced through the autonomic nerves between the glycogenic center and the liver. Glycosurias are not infrequently observed following head trauma or in connection with brain tumor, meningitis, tabes, etc., which are probably caused by a similar mechanism to that at play in the *piqûre*.

Various *drugs* (phosphorus, carbon monoxid, hydrazine, arsenic, etc.) cause glycosurias that are apparently due to discharge of sugar from stored glycogen (Woodyatt).

Glycosuria may be caused by administration of the *extracts of certain ductless glands;* the adrenal, the thyroid and the hypophysis. According to Eppinger, Falta and Rudinger epinephrin and thyroid secretions influence the *mobilization* of sugar from glycogen in the liver being opposed in this effect to the action of the pancreas, which, according to their doctrine, limits the formation of sugar from glycogen as well as from protein and fat.

Glycosuria of Diabetes mellitus.—In diabetes the glycosuria is due to the defects in the oxidation of the sugar and in the glycogen storage mechanism that close the normal outlet for the sugar of the diet and that formed in the body. This sugar that cannot be burned, nor all held in storage as glycogen, accumulates in the blood and is excreted in the urine. The source of the defect in oxidation and storage is intimately associated with disturbances in the internal secretion of the pancreas (*vide* Diabetes, Part XIII).

Glycosuria in Phloridzin Diabetes.—Essentially different from the already mentioned types of glycosuria is that which follows the administration of phloridzin (a glucoside from bark of apple, pear, plum and cherry trees). In this type there is no hyperglycemia, and the passage of glucose into the urine is to be attributed either to an abnormal permeability of the renal filter or to some pathological physicochemical state of the blood sugar, which leads to its excretion. The first hypothesis is generally accepted as correct, and the term *renal diabetes* is frequently applied to the condition.

Transient and Permanent Glycosurias.—For clinical purposes it is convenient to classify the glycosurias into the transitory and the more permanent glycosurias. The transitory glycosurias include all those above mentioned as due to diet, nervous influences, drugs and internal secretions, as well as cases of true diabetes in the early stages. "In general, experience teaches that all persistent glycosurias prove to be diabetic" (Woodyatt).

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iii. Qualitative Tests for d-Glucose in the Urine

1. General Remarks on the Recognition of Sugar in the Urine

The amount of d-glucose present in the total 24 hour urine may vary from a trace to several hundred grams. It is customary to include a qualitative test for sugar in all urinary examinations, but in the study of a case of glycosuria it is the quantitative methods that are of chief importance.

The detection of d-glucose in the urine is complicated by the necessity of differentiating this body from other carbohydrates that may be

present there, and from certain non-carbohydrate urinary constituents that obscure the results of the tests employed.

The properties of d-glucose upon which the tests used are based are the following:

1. It reduces metallic hydroxides; *e. g.,* cupric hydroxid to red cuprous oxid; bismuth subnitrate to black metallic bismuth.
2. On fermentation with beer yeast (*Saccharomyces cerevisiae*) it yields alcohol and CO_2.
3. It rotates the plane of polarized light to the right (dextrorotation).
4. On treatment with phenylhydrazin it yields yellow crystals of glucosazon.

As will be seen from the appended table these properties are possessed to some extent by all carbohydrates. The occurrence of a positive result with one test does not therefore enable us to affirm with certainty the presence of d-glucose. A sufficient number of the other properties of d-glucose should be tested to make the identification complete.

In clinical practice, it is the almost universal custom to test the urine, as a routine measure, by one of the reduction tests. If such a test be negative, the absence of carbohydrates in pathological amounts is proven. On the other hand, if a positive result is obtained, it is first necessary to rule out the possibility of the reduction having been due to certain non-carbohydrate reducing bodies in the urine, and, when this has been done, to determine, by further tests, which of the several reducing carbohydrates is the one present.

The *non-carbohydrate bodies* present in the urine that may cause confusion in the various copper or bismuth tests are named with each test as sources of error. They fall, in general, into four classes; (1) preservatives added to the urine (chloroform, formaldehyd), (2) certain normal and abnormal metabolic products (glycuronates, urinary pigments, homogentisic acid, etc.), (3) drugs excreted in the urine (benzoic acid, rheum, sulphonal, urotropin), (4) albumin if present in more than traces.

The possibility of error due to the presence of these bodies should always be kept in mind. Where chloroform has been used as a preservative it must be removed by boiling. The reduction caused by non-carbohydrate bodies of metabolic origin may be recognized by its atypical character or by the reactions given with other tests. The same holds true with the results due to drugs. Urochrom, uric acid, creatinin and glycuronic acid derivatives can be almost completely removed from the urine by treating 20 c.c. of urine with 5 c.c. of 25 per cent HCl and 2 grams of Merck's blood charcoal. The mixture is shaken a few times during five minutes and filtered. Albumin should be removed by the heat and acetic method.

If every positive or doubtful test is made the subject of further investigation error will not occur.

TABLE DIFFERENTIATING THE MORE IMPORTANT SUGARS THAT OCCUR IN THE URINE
[Sydney Miller]

Reducing Bodies in the Urine.	Fehling's and Trommer's.	Nylander's Solution.	Fermentation.	Polarization.	Phenylhydrazin	Melting-Point of Osazon.	Rotation of Osazon.	Remarks
Glucose	✢	✢	✢	Dextro. 52.7°	✢	205°	Laevo. 1'32"	
Levulose	✢	✢	✢	Laevo. 92°	✢	205°	Laevo. 1'30"	Seliwanoff's test.
Lactose	Reducti ✢	on slow ✢	○	Dextro. 52.5°	Negative in the Urine	200°	Inactive	Phenylhydrazin + after concentration and extraction.
Pentose	Reducti ✢	on slow ✢	○	Inactive	✢	153°–160°	Inactive	Phloroglucin } tests Orcin } +
Maltose	✢	✢	✢	Dextro. 138°	✢	206°	Dextro. 1'30"	Ferments after hydrolysis.
Conjugated Glycuronic Acid	✢	✢	○	Dextro-Laevo after Hydrolysis	✢ after Hydrolysis	115°	?	Phloroglucin +; Orcin + after hydrolysis.
Homogentisic Acid of Alkaptonuria	✢	○	○	○	○	○	○	Urine blackens with exposure and alkalis, reduces ammon. $AgNO_3$ in the cold.
Chloroform	Atypical ✢	○	○	○	○	○	○	Urine previously boiled does not reduce.

2. *Tests for d-Glucose Depending Upon the Reduction of Salts of Copper or of Bismuth*

Benedict's Qualitative Reduction Test

REAGENT.—The formula of Benedict's reagent is as follows:

Copper sulphate (C. P. crystallized)	17.3 grams
Sodium or potassium citrate	173.0 grams
Sodium carbonate (crystallized)	100.0 grams
Distilled water q. s. ad.	1,000.0 c.c.

The citrate and carbonate are dissolved in about 700 c.c. of water by the aid of heat (filter if necessary). The copper sulphate is dissolved in about 100 c.c. of water. The two solutions are mixed; the mixture is cooled and made up to 1 liter.

TECHNIC.—If more than a trace of albumin is present in the urine, it is removed by the heat and acetic method. Eight or ten drops of the urine (not more) are then added to five c.c. of the reagent in a test tube and the mixture is then boiled vigorously for one or two minutes. Glucose will cause the appearance of a *red, yellow,* or *greenish* precipitate that fills the whole solution. If only a trace of glucose be present the precipitate appears only on cooling. If glucose is absent, the solution remains clear or shows only a faint bluish turbidity.

Sources of Error.—This solution is reduced by *alkapton acids* and by *conjugated glycuronic acids*. These bodies must therefore be ruled out by suitable tests (*vide* table). It has, however, the advantage of not being affected by creatinin or uric acid, nor by such preservatives as chloroform, chloral or formaldehyd, which introduces error into other tests. It is said to be ten times more sensitive to urinary sugar than the other copper tests, which it is supplanting in many laboratories (Allen, Webster).

Fehling's Qualitative Reduction Test.—Reagents.—Two solutions are necessary for the performance of this test.

SOLUTION I

Copper sulphate (C. P. crystallized)	34.64 grams
Distilled water q. s. ad.	500.00 c.c.

The crystals are dissolved in a few hundred c.c. of water and water then added to the solution exactly to the 500 c.c. mark in a volumetric flask.

SOLUTION II

Rochelle salt	173 grams
Sodium hydrate	50 grams
Distilled water q. s. ad	500 c.c.

The Rochelle salt and sodium hydrate are first dissolved in a part of the water and water then added to bring the volume to exactly 500 c.c.

These solutions can be used for both quantitative and qualitative work.

Technic.—Reducing preservatives must be avoided (chloroform may be removed by boiling). Albumin should be removed if more than a trace is present. Two c.c. each of Solution I and Solution II are placed in a clean test tube and the mixture boiled. No precipitate should form; if a red precipitate forms the solutions are at fault and fresh ones should be prepared. Add to the boiling mixture not more than one c.c. of urine. A yellow or red precipitate forms at once in the presence of glucose. Boiling must not be continued after addition of the urine.

Sources of Error.—These are very numerous. The solutions are reduced by preservatives, chloroform, chloral, formaldehyd. In concentrated urines the urinary pigments, creatinin, and uric acid may affect the reduction. Homogentisic acid, numerous drugs (acetphenetidin, benzoic acid, chloral, phenacetin, salol, salicylic acid, sulphonal, etc.) also cause confusing reductions. Most of these non-carbohydrate reductions give a dirty greenish yellow precipitate; it is important, however, to test all such urines by other methods, as small amounts of d-glucose may be masked under these atypical reductions.

The test is that most widely used, but is open to many objections and is less convenient than Benedict or Haine's. It is said to indicate 0.08 per cent of d-glucose.

Haine's Qualitative Reduction Test.—Reagents.—The solution used is as follows:

Copper sulphate (C. P. crystallized)	12 grams
Potassium hydrate	45 grams
Glycerin	90 c.c.
Distilled water q. s. ad.	1,000 c.c.

A slight deposit may occur on standing, but this does not affect the value of the solution for qualitative work. The clear supernatant fluid is decanted as required. The great advantage of this solution lies in its permanence as compared to the mixture of Fehling's solutions.

Technic.—Reducing preservatives must be avoided (chloroform may be removed by boiling). More than a trace of albumin should be removed. Four or five c.c. of the solution are gently boiled in a test tube. Three to ten drops of the urine (not more) are added. In the presence of d-glucose a yellow or yellowish red precipitate occurs. The solution is not to be boiled after adding the urine.

Sources of Error.—These are practically the same as mentioned under Fehling's test. The advantage of the test lies in the need of only one solution, and that one permanent. It is less delicate than Benedict's solution.

Nylander's Qualitative Bismuth Reduction Test.—Reagent.—The solution is made up as follows: Four grams of Rochelle salt are dissolved in 100 c.c. of ten per cent sodium hydrate solution with gentle heat, and as much bismuth subnitrate is added as will dissolve (about 2 grams). After the mixture is cooled the undissolved bismuth subnitrate is filtered off. The filtrate should be kept in a dark bottle, where it will remain permanent for a long time.

Technic.—Albumin, if present, should be removed, as it interferes decidedly. To 5 c.c. of urine add ½ c.c. of the reagent. Place the tube containing the mixture in a boiling water bath for *five minutes* (not longer). In the presence of d-glucose the fluid in the tube turns dark and a black precipitate of metallic bismuth separates. The separation may be quite gradual during the boiling; but if the fluid turns dark only on cooling, the test should be called negative. A whitish or yellowish precipitate is of no significance.

Sources of Error.—Like Fehling and Haine's solutions, the bismuth test is affected by urinary pigments, glycuronates, preservatives and many drugs (urotropin, antipyrin, benzoic acid, chloral, salol, senna, sulphonal, trional). It is, however, not affected by certain bodies that are common causes of atypical reductions with the copper reduction tests, viz., uric acid, creatinin, pyrocatechin and phosphates. In many instances, therefore, it is useful as a control test. A negative Nylander test in a protein free urine is reliable proof of the absence of pathological amounts of sugar. It detects as little as 0.08 per cent of glucose.

Fig. 436.—Fermentation Tube; Small Size; on Glass Foot; Ungraduated. By courtesy of A. H. Thomas Co., Phila.)

3. *Fermentation as a Qualitative Test for Glucose*

Principle.—Glucose not only yields the reduction tests above mentioned, but, unlike many reducing substances, it ferments with yeast. If a reducing substance found in the urine also ferments, it is almost certainly either glucose or levulose.

Technic.—To 20 c.c. of urine in a test tube, boiled and cooled, add a piece of freshly compressed yeast the size of a pea and shake gently until the yeast is finely divided. Pour the mixture into an ordinary fermentation tube and place in the incubator for a few hours. As a control, two other tubes are examined at the same time, one containing distilled water (or normal urine) alone with yeast, the other containing .5 per cent glucose solution with yeast, or normal urine to which a little glucose has been added with yeast. In the tubes containing

glucose, CO_2 gas will accumulate. The test is delicate for from 0.1-0.5 per cent of glucose. With ordinary commercial yeast a slight amount of gas usually develops in control tubes.

Care must be taken when preparing the yeast mixture not to shake violently enough to include air. Bacterial fermentation is prevented by sterilizing the urine by boiling and then cooling before adding the yeast.

4. Qualitative Test for d-Glucose With the Polariscope

As a qualitative test for d-glucose, the chief value clinically of polariscopic examination is as a secondary method *for the differentiation of d-glucose from non-carbohydrate reducing bodies in the urine and from levulose.* The non-carbohydrate reducing substances, glycuronic acid, chloroform, creatinin, etc., are either optically inactive or feebly levorotatory, as is, of course, levulose. On the other hand other sugars besides d-glucose may be the cause of dextrorotation, (lactose, maltose) which is, therefore, in no way specific for d-glucose.

Technic.—See Quantitative Determination of Glucose.

5. Qualitative Phenylhydrazin Test for d-Glucose (Cippolina's Modification)

Principle.—The formation of *osazones* on treatment with phenylhydrazin and dilute acetic acid is a property characteristic of carbohydrates. These osazone crystals show properties (morphology, melting point, optical activity) that are more or less specific for the carbohydrate concerned. The complete test therefore includes preparation of the crystals, microscopic study of their morphology, determination of their melting point and of their specific rotation. Since, however, in clinical practice only the first two steps are commonly used, the reader will be referred to larger handbooks for the other methods.

Technic.—Albumin should be first removed, if present. Five drops of pure fluid phenylhydrazin (the base), and 0.5 c.c. of glacial acetic acid are added to 4 c.c. of the protein free urine. The mixture is *gently boiled* for one minute. Four or five drops of sodium hydrate (sp. gr. 1.160) are now added. The mixture should remain acid. The tube is set in a rack. Within twenty minutes the characteristic sheaflike yellow crystals of phenylglucosazone appear. A little of the urine containing the crystals is then examined on a clean slide under the microscope. If atypical forms are present, recrystallization from hot 60 per cent alcohol should be used to purify the crystals (see Fig. 2, Pl. XVIII).

Sources of Error.—Atypical crystals may be obtained from normal urine tested in the above manner (Moritz, Geyer, Salkowski). After treatment of the urine with HCl, Cammidge has found the presence of an osazone as a characteristic of pancreatic disease. The crystals showing the morphology described for glucosazone are, however, practically specific for the presence of a carbohydrate and in all probability of d-glucose. The test is most valuable as a confirmatory one. It is said to yield a positive reaction with 0.02 per cent of d-glucose.

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iv. Quantitative Methods for the Determination of d-Glucose in the Urine

A large number of quantitative methods of sugar determination have been worked out. For clinical purposes the methods that utilize polarization, fermentation and titration suffice.

1. Quantitative Determination of d-Glucose by Polarimetry

When optically active substances other than sugar are absent and the amount of sugar is not less than 0.3 per cent, no method of quantitative estimation is better than the polarimetric. When possible it is well to use simply filtered urine for the examination.

Technic.—Often the urine must be first decolorized by normal lead acetate. To 25 c.c. of urine add 5–10 drops of glacial acetic acid and then as much finely powdered normal *lead acetate* as will go on the point of a knife. Shake well and filter into a vessel previously washed with distilled water and dried. If

only a small quantity of urine is available, 10 to 12 c.c. may be rubbed up with 2 grams of finely powdered normal lead acetate in a small porcelain mortar. On filtration a nearly colorless solution will be obtained in amounts large enough for polarization in the newer tubes, which are only 2 dcm. long and contain 5–6 c.c.

When albumin is present in amounts greater than a trace, it is best removed by the following method. Add acetate of lead to the urine, filter, warm the filtrate several minutes with lead hydrate; pass H_2S gas through the solution, filter, drive off the acetic acid by heat. When facilities are not at hand for this method the

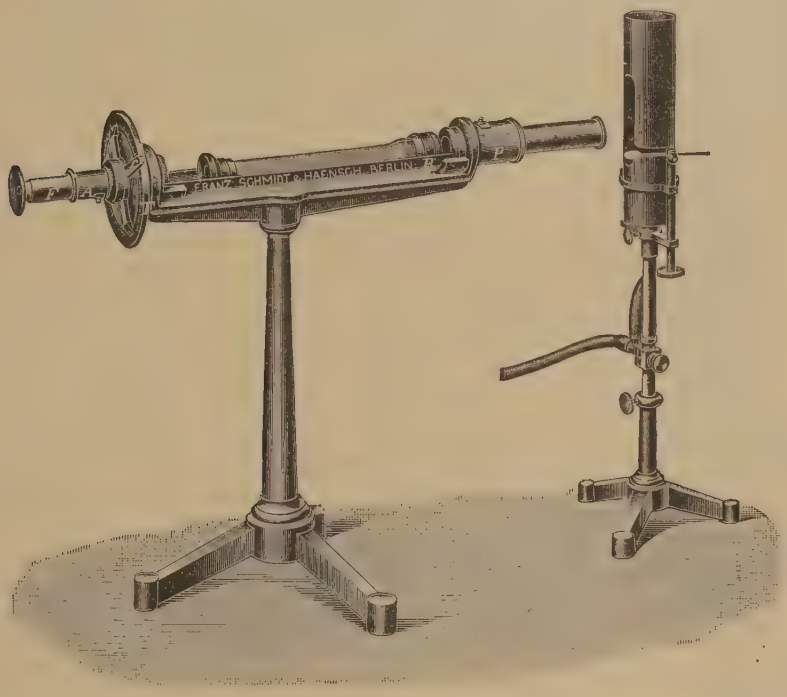

Fig. 437.—Polariscope (Schmidt and Haensch, Mitscherlich, with Laurent Polarizer) for Direct Reading. The Sugar Content of the Urine Can Be Read Off Directly; Accurate to 1/10 of 1 per cent. (By courtesy of A. H. Thomas Co., Phila.)

albumin may be removed by heat and acetic acid. The freeing of glycuronic acid by this method introduces, however, a small error.

The specific rotation of d-glucose for yellow sodium light (α) is $+ 52.8°$. From the degree of deviation (α) in the special case, and the length l of the tube used *expressed in decimeters,* it is easy to calculate the percentage (p) of glucose in the urine according to the formula $p = \alpha \times \frac{100}{52.8} \times l$.

If a tube of 18.8 cm. long be available, the number read off on the scale, in degrees, gives without calculation the percentage of sugar present. In some instruments, the scale of the apparatus is not expressed in degrees and minutes, but in percentages of sugar (saccharometer).

The figures above given are, of course, for d-glucose. If other sugars are present and glucose is absent the amounts may be calculated approximately as follows:

Arabinose by division with +2.
Fructose by division with —1.8.
Galactose by division with + 1.55.
Maltose by division with + 2.6.
Saccharose by division with + 1.26.
Free glycuronic acid by multiplication with + 2.8.
Lactose has the same rotation as glucose.

If *beta-oxybutyric acid* be present, the results of polarization will be too small owing to its levorotation, but can be corrected by polarizing again after fermentation and adding the degrees of levorotation (due to the oxybutyric acid) to the dextrorotation found before fermentation. This gives the full amount of dextrorotation due to the d-glucose.

Fig. 438. — The Lohnstein Precision-Saccharometer for the Accurate Determination of Sugar in Undiluted Urine. (By courtesy of A. H. Thomas Co., Phila.)

Polarimetry is the most convenient method for quantitative determination of sugar clinically, especially in hospital work.

2. *Quantitative Determination of d-Glucose by the Fermentation Method*

An approximate estimation of the sugar present can be made by carefully taking the specific gravity before and after fermentation (standardized hydrometer, pyknometer).

Roberts' Method.—The urine must be acid. The specific gravity is first taken. The urine is then allowed to ferment with yeast (*a piece the size of a bean*) in a long-necked flask for 24 hours at room temperature, the mouth of the flask being covered by a watch-glass to prevent evaporation. A trace of sodium fluorid may be added to prevent bacterial action. At the end of this time, the specific gravity of the filtered urine is determined. For every degree by which the specific gravity is lowered we may calculate a sugar content of 0.23 per cent; thus if the urine before fermentation had a specific gravity of 1,040 and afterward a specific gravity of 1,020, the sugar content is 4.6 per cent.

Fermentation in Lohnstein's Saccharometer.—This instrument is very convenient and yields results almost as exact as those obtained by titration.

In the bulb of the apparatus, place 12 c.c. of mercury. On the surface of the mercury, place 0.5 c.c. of urine with a pipet, and add yeast (rubbed up with 2 or 3 volumes of water). The stopper is now greased, and so placed that the two holes are opposite one another. With a needle, the opening is cleared so that air can enter. The scale is now put in place, and the quicksilver adjusted to the zero point by slightly tipping the apparatus. The stopper is next turned to shut off the air and a weight placed on the stopper to prevent leakage during gas formation. The urine is then left to ferment at the room temperature for 24 hours, or

in the incubator for 6 hours. The amount of sugar may be read off on the scale. The instrument should be at room temperature when the reading is made.

Another good saccharometer is that of A. Basler.

3. *Quantitative Determination of d-Glucose by Titration Methods*

Many methods are in use for the determination of sugar by titration. The two here given are probably the best.

Benedict's Second Method.—Reagent.—As opposed to the first method advocated by this author only one solution is used. The formula for this reagent is as follows:

Copper sulphate (C. P. crystallized)	18.0 grams
Sodium carbonate (anhydrous)	100.0 grams
Sodium citrate	200.0 grams
Potassium sulphocyanate	125.0 grams
Potassium ferrocyanid (5 per cent solution)	5.0 c.c.
Distilled water q. s. ad	1,000.0 c.c.

The citrate, carbonate and sulphocyanate are dissolved by the aid of heat in about 800 c.c. of water. The solution is filtered. The copper sulphate is separately dissolved in about 100 c.c. of water and this solution is poured into the first, slowly, and with constant stirring. The cooled ferrocyanid solution is now added to the mixture and distilled water run in sufficient to bring the volume to exactly 1,000 c.c. The weighing and manipulation of the copper sulphate must be quantitatively accurate. Less precision is necessary with the other constituents.

Technic.—Ten or fifteen c.c. of urine are diluted accurately 1:10. Chloroform, if present, must be removed by boiling. With a volumetric pipet 25 c.c. of the reagent are placed in a porcelain evaporating dish (25–30 cm. in diameter). Five to ten grams of anhydrous sodium carbonate and a very small quantity of powdered pumice stone are now added. The mixture is boiled over a free flame till the carbonate is dissolved. The diluted urine is run in from a buret until a heavy white precipitate (cuprous sulphocyanid) is formed and the blue color of the solution has perceptibly faded. Diluted urine is then again slowly added with constant boiling until all blue color has disappeared. This marks the end-point of the reaction. Twenty-five c.c. of the reagent are reduced by 0.05 grams of d-glucose (0.053 grams of levulose). From the amount of urine run in, the sugar content of the total 24-hour urine is easily calculated. Should the mixture become concentrated during the titration, distilled water should be added to replace that lost by evaporation.

Bang's Method.—Reagents.—Two solutions are necessary for this method:

SOLUTION I

Potassium bicarbonate	100 grams
Potassium carbonate	500 grams
Potassium sulphocyanate	400 grams
Copper sulphate (C. P. crystallized)	25 grams
Distilled water q. s. ad	2,000 c.c.

In a two-liter volumetric flask about 1,300 c.c. of water are placed. In this are dissolved, in succession, the bicarbonate, the carbonate and the sulphocyanate. The copper sulphate (quantitative weighing) is dissolved separately in about 150 c.c. of water, and after cooling, this solution is added quantitatively to the solution in the volumetric flask. Water is now filled in to exactly the 2-liter mark. After the mixture has stood 24 hours it is filtered. It is stable for about three months.

SOLUTION II

Potassium sulphocyanate	200 grams
Hydroxylamin sulphate	6.55 grams
Distilled water q. s. ad	2,000 c.c.

The sulphocyanate is dissolved in about 1,500 c.c. of water in a 2-liter volumetric flask. The hydroxylamin sulphate (quantitative weighing) is dissolved separately in a few hundred c.c. of water and this solution is added quantitatively to the sulphocyanate solution. Water is then filled in exactly to the 2-liter mark. The solution, if kept in a dark bottle, is permanent.

Technic.—In this test an excess of copper-sulphate is used and the non-reduced portion is determined by titration with Solution II. If the urine is high colored it is treated with HCl (5 c.c. of 25 per cent HCl to 20 c.c. urine) and shaken for 5 minutes with 2 gms. Merck's blood charcoal and filtered through a dry filter. The cleared urine is then diluted 1:2 (unless less than 0.6 per cent sugar is present). Ten c.c. of the diluted or undiluted urine are accurately measured into a 200 c.c. Jena Erlenmeyer flask. Exactly 50 c.c. of the copper solution (Solution I) are added. The flask is then heated on a wire gauze to boiling and boiled steadily and moderately for *exactly 3 minutes*. It is then quickly cooled to room temperature by immersion in cold water. The contents are then titrated with the hydroxylamin solution (Solution II) until all blue color has disappeared. From the number of c.c. of the hydroxylamin solution used the sugar content in milligrams of the urine used is calculated from the accompanying table.

BANG'S TABLE OF REDUCTION EQUIVALENTS

Cubic Centimeters of Hydroxylamin Solution	Milligrams of Sugar	Cubic Centimeters of Hydroxylamin Solution	Milligrams of Sugar
0.75	60.0	25.50	23.5
1.00	59.4	26.00	22.9
1.50	58.4	26.50	22.3
2.00	57.3	27.00	21.8
2.50	56.2	27.50	21.2
3.00	55.0	28.00	20.7
3.50	54.3	28.50	20.1
4.00	53.4	29.00	19.6
4.50	52.6	29.50	19.1
5.00	51.6	30.00	18.6
5.50	50.7	30.50	18.0
6.00	49.8	31.00	17.5
6.50	48.9	31.50	17 0
7.00	48.0	32.00	16.5
7.50	47.2	32.50	15.9
8.00	46.3	33.00	15.4
8.50	45.5	33.50	14.9
9.00	44.7	34.00	14.4
9.50	44.0	34.50	13.9
10.00	43.3	35.00	13.4
10.50	42.5	35.50	12.9
11.00	41.8	36.00	12.4
11.50	41.1	36.50	11.9
12.00	40.4	37.00	11.4
12.50	39.7	37.50	10.9
13.00	39.0	38.00	10.4
13.50	38.3	38.50	9.9
14.00	37.7	39.00	9.4
14.50	37.1	39.50	9.0
15.00	36.4	40.00	8.5
15.50	35.8	40.50	8.1
16.00	35.1	41.00	7.6
16.50	34.5	41.50	7.2
17.00	33.9	42.00	6.7
17.50	33.3	42.50	6.3
18.00	32.6	43.00	5.8
18.50	32.0	43.50	5.4
19.00	31.4	44.00	4.9
19.50	30.8	44.50	4.5
20.00	30.2	45.00	4.1
20.50	29.6	45.50	3.7
21.00	29.0	46.00	3.3
21.50	28.3	46.50	2.9
22.00	27.7	47.00	2.5
22.50	27.1	47.50	2.1
23 00	26.5	48.00	1.7
23.50	25.8	48.50	1.3
24.00	25.2	49.00	0.9
24.50	24.6	49.50	0.5
25.00	24.1	50.00	0.0

For every 1/10 c.c. hydroxylamin solution used more than is given in the table, subtract 0.1 mg. if the reading be between 49 and 15, while if it be between 15 and 1 subtract 0.2 mg.

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(*b*) *Pentoses in the Urine* (*Pentosuria*)

i. Occurrence of Pentosuria

The tolerance of the normal body for pentoses administered by mouth is very slight and it is probable that traces of pentose are not infrequent in normal urine arising from pentoses in fruits, etc., of the diet (*alimentary pentosuria*).

A small group of cases has been reported in which the interesting abnormality was observed of a *continuous pentosuria* apparently of endogenous origin since it continued even during starvation. Outputs as high as 36 grams a day have been recorded. The disease has been found in several members of the same family. No ill-effects have been observed. The source of the pentose is still quite unknown.

The urine in pentosuria reduces copper solutions but the reduction is very slow. It reduces the bismuth salt, but atypically, with the formation of a gray instead of a black precipitate in Nylander's test. No fermentation occurs with yeast. The urine containing pentose alone is optically inactive. These properties together with the characteristic production of furfurol on distillation in the presence of acids are sufficient to detect pentose in the urine (See Glycuronic Acid).

ii. Qualitative Methods for the Detection of Pentose in the Urine

Careful chemical studies should be made of the pentoses in the urine to determine their nature. Recent studies of the nucleic acids, of guanylic acid and of inosinic acid have shown that the pentose group in these substances is *d-ribose*. It is probable that this is the only pentose of normal human metabolism. Probably other pentoses are excreted when fruits are eaten (See Nucleic Acid Metabolism, Part XIII).

1. Bial's Orcin Test for Pentoses

Bial's reagent consists of 12 drops of 10 per cent ferric chlorid, plus 0.5 gm. orcin, in 250 c.c. HCl (30 per cent). Five c.c. of this reagent are heated to boiling in a test tube and then removed from the flame. A few drops of the urine are added; not more than 1 c.c. A green color should appear *at once* if pentose is present. If performed in this manner the test is not given by combined glycuronates.

2. Phenylhydrazin Test for Pentoses

The method is used in the same way as described under tests for glucose (*q. v.*). If glucose and pentose are simultaneously present in the urine, their osazones may be separated by digesting with water, not over 60° C. in temperature, when the pentosazones will be dissolved. If the pentosazone crystals be dissolved in 20 c.c. of water and 5 c.c. conc. HCl and this mixture be distilled, the distillate will give a beautiful reaction with Bial's reagent, which absolutely eliminates glycuronic acid, the substance most likely to be confused with pentose.

Should a pentose be discovered in the urine, it is desirable to prepare it in amounts large enough to permit of purification and exact chemical identification. The methods used by Levene in the identification of d-ribose may be used as a paradigm (See Nucleic Acids, Part XIII).

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(c) *d-Fructose in the Urine (Fructosuria; Levulosuria)*

i. Occurrence of Fructosuria

The appearance of d-fructose, often called levulose, in the urine is comparatively rare. The normal tolerance for this sugar is low (1.3 gm. per kilo of body weight); but the amounts of levulose in the ordinary diet are well within the limits of this tolerance.

In a few cases a *spontaneous alimentary levulosuria* has been observed. The tolerance for this sugar was apparently so lowered in these cases that even the small amounts present in the diet were not utilized and they appeared in the urine (2.7 to 24 gms.). On a carbohydrate free diet the urine was levulose free. The tolerance for levulose is apparently due to some function of the liver and a determination of this tolerance has been used clinically with some success as a *hepatic functional test.*

In many cases of severe diabetes, levulose is excreted as well as glucose (mixed melituria). It is possible that this is to be explained by the disturbances in hepatic function often associated with diabetes (Woodyatt). The clinical importance of the phenomenon is not great aside from the danger of error in polariscopic determinations.

ii. Properties of d-Fructose

Levulose has the same reducing action as d-glucose; it ferments; it forms a phenylosazon almost identical with that of d-glucose. It differs from d-glucose in being strongly levogyrate, in forming a characteristic osazone with phenylmethylhydrazin, and in yielding Seliwanoff's reaction. These characteristics are sufficient for clinical identification.

A pure levolusuria detected by the reduction test will be identified

by the results of the polariscopic test, and of Seliwanoff's test. When both levulose and glucose are present the results of the quantitative reduction test will represent the sum of their similar reducing powers whereas the polariscope will show only such rotation as results from the addition of their opposed powers of rotation. Such a situation points to the presence of a levogyrate body. The fermentation test will remove both the reducing power and the optical properties of such urine (such as are not due to β-oxybutyric acid, glycuronic acid, albumin and other levogyrate bodies), showing that the levogyrate body is also fermentable. The application of Seliwanoff's test will identify the body as levulose.

iii. Qualitative Methods for the Detection of d-Fructose (Levulose) in the Urine

1. Seliwanoff's Test for d-Fructose

Technic.—To 10 c.c. of urine add an equal volume of 25 per cent HCl and a few crystals of resorcin. The mixture is boiled *gently* for a few seconds. A bright red color should appear if levulose is present; glucose gives no coloration.

The solution is now cooled in an evaporating dish, alkalinized with sodium carbonate in substance and then extracted by shaking in a test tube with acetic ether (ethyl-acetate). The ethyl-acetate extract should be colored yellow with a faint greenish fluorescence if levulose is present; and this color should become rose red on addition of alcohol (Borchardt).

Sources of Error.—Santonin or rhubarb taken medicinally may interfere with the test. Indican in large quantities interferes with the coloration of the acetic ether. It should be removed by treating the urine with an equal volume of Obermayer's reagent (*q. v.*) and repeatedly extracting the indigo with chloroform until the blue color is all gone. Then dilute the urine with two volumes of water and proceed with the test.

2. The Osazone Test for d-Fructose

The phenylhydrazin test is of no use in the differentiation of levulose and glucose as their osazones are practically identical in appearance, melting point and specific rotation. On the other hand, Neuberg has shown that levulose forms an osazone with *phenylmethylhydrazin,* while glucose does not form such a compound. Positive identification can, therefore, be made in this way. The method, however, is so seldom necessary, on account of the rarity of spontaneous fructosuria, that it will not be described here.

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(*d*) *Lactose in the Urine (Lactosuria)*

i. Occurrence of Lactosuria

The clinical importance of the appearance in the urine of the disaccharide, lactose, is derived from its comparatively frequent occurrence during *lactation* and the danger of mistaking this apparently innocuous phenomenon for a diabetic glycosuria. The excretion of lactose in the urine may reach 2–3 per cent in the early days of the puerperium and may persist for some time.

Alimentary lactosuria has been observed in children with gastro-intestinal disturbances. In these cases the tolerance for lactose is definitely diminished. The nature of the assimilatory defect is not known.

ii. Properties of Lactose

Lactose reduces copper and bismuth solutions. It does not ferment, but if subjected to bacterial hydrolysis it yields glucose and galactose, the former of which will show fermentation. Hence the fermentation test should be judged at the end of a few hours; yeast fermentation should at this time yield negative results that will not yet be affected seriously by bacterial action. Lactose is optically active (+52.5), having practically the same specific rotation as d-glucose (+52.7). It forms a lactosazon, which has a melting point of 200° C. and is optically inactive.

iii. Qualitative Methods for the Detection of Lactose in the Urine

The recognition of lactosuria depends upon finding a reducing body in the urine that is dextrorotatory but does not ferment in 12 hours. After the urine has been boiled with 2 per cent H_2SO_4 and then neutralized (lactose hydrolyzed to glucose and galactose), it will be found to be fermentable. Rubner's test and the phenylhydrazin test are confirmatory.

1. Rubner's Test for Lactose

Ten c.c. of urine are treated with an excess (3 grams) of lead acetate and boiled for a few minutes. The solution is then filtered and ammonia added to the

filtrate until a slight permanent precipitate remains. An intense brick red color followed by the deposition of a *cherry red precipitate* occurs in the presence of lactose. Glucose may cause a red color in the fluid, but the precipitate is yellow.

2. *Phenylhydrazin Test for Lactose*

This consists in the use of phenylhydrazin for the preparation of lactosazone crystals, and the optical activity and the melting point of the latter are tested. The test is facilitated by concentrating the urine to a small bulk and extracting the residue with alcohol. The alcohol is evaporated and the residue taken up with water. This watery solution is used for the phenylhydrazin test (see Phenylhydrazin Test for Glucose). The distinctive feature is the specific rotation of the crystals. The crystals are purified by repeated recrystallization from hot 60 per cent alcohol. Then 0.2 gm. of the pure crystals are dissolved in 4 c.c. of pyridin. Six c.c. of absolute alcohol are added and the solution is examined polariscopically in the 100 mm. tube. As opposed to crystals of glucosazone the lactosazone crystals are not optically active.

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(e) *Maltose in the Urine* (*Maltosuria*)

This is very rare but is occasionally met with in diabetes and sometimes in pancreatic disease. Unless considerable quantities are present, the recognition of the condition is very difficult.

The maltose molecule, on boiling with dilute mineral acid, or through the action of enzymes (*maltase*), splits into 2 molecules of d-glucose. It is easily fermented by yeast. With the phenylhydrazin test, it yields *osazon* crystals (M. P. 202–208°), which, unlike those derived from glucose, are soluble in hot water.

To recognize it in urine, we make use of the difference between polarization and reduction, since the amounts (calculated as glucose) obtained by the former are larger than by the latter. If one boil the urine with dilute acid, each maltose molecule is changed into two d-glucose molecules (see above) and the rotation of polarized light becomes less, the reduction of copper salts greater.

(f) *d-Galactose in the Urine* (*Galactosuria*)

This is often present in the urine of sucklings, along with lactose. Its *rotary power* is $(\alpha)\ D = +81.3°$. It *ferments* completely, but more slowly than glucose. It yields the *reducing* reactions.

To recognize it in urine, the phenylhydrazin test is necessary. It yields a

galactosazon that is characteristic; its M. P. is 188–193° C.; its specific rotary power in Neuberg's pyridin alcohol mixture is (α) D = +0.48.

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(*g*) *Glycuronic Acid in the Urine*

i. Occurrence

Glycuronic acid occurs in the urine conjugated with various substances. Many of these bodies are apparently detoxicated by means of this conjugation. In normal urine only small amounts of glycuronic acid occur (0.004 g. in 100 c.c.). The amounts may be much increased after medication with chloral, carbolic acid, morphin, acetanilid, antipyrin, pyramidon, etc. Abnormally large amounts are excreted also in *intestinal obstruction* along with phenol and indoxyl. Further, in *diabetes mellitus, in CO-poisoning* and in some forms of *dyspnea,* larger amounts appear in the urine.

A urine that contains conjugated glycuronic acids *reduces* copper, *does not ferment* with yeast, and *rotates* polarized light to the left. After boiling with strong HCl, the levorotation disappears, or changes to dextrorotation because the glycuronic acid is set free. On boiling with orcin and HCl, the urine turns green.

ii. Qualitative Method for the Detection of Glycuronic Acid in the Urine

1. The Naphthol Resorcin Test (Tollens)

Technic.—To 5 c.c. of urine add ½ to 1 c.c. of a 0.5 per cent alcoholic solution of naphthol resorcin and 5 c.c. conc. HCl (sp. gr. 1.19). Boil over a low flame for one minute. The fluid becomes dark. The tube is set aside for four minutes, after which it is cooled completely by shaking under the water-tap. An equal volume of ether is now added and the test tube shaken vigorously. Addition of a few drops of alcohol will aid in the separation of the ether. If glycuronates are present the ether extract is faint blue to violet color and when examined spectroscopically it will show a single dark band near the sodium line. This test is not positive with pentose.

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6. Acetone Bodies in the Urine (Acetonuria; Diaceturia; Ketonuria)

(*a*) *Sources of the Acetone Bodies (Their Relation to Acidosis)*

The *acetone bodies* include β-oxybutyric acid, diacetic (aceto-acetic) acid, and acetone. They are chemically closely related. Oxidation of *β-oxybutyric acid* yields *diacetic acid,* and this, on further oxidation, yields *acetone* with liberation of CO_2.

$$CH_3-CHOH-CH_2-COOH = \beta\text{-oxybutyric acid}$$
$$\downarrow\uparrow$$
$$CH_3-CO-CH_2-COOH = \text{diacetic acid}$$
$$\downarrow$$
$$CH_3-CO-CH_3 \quad = \text{acetone}$$
$$+$$
$$CO_2$$

These bodies are probably formed in normal intermediary metabolism. Their chief *source* is apparently from the fats, but they may also arise to some extent from the fatty acids resulting from the deaminization of amino-acids. In normal metabolism, they are burned to CO_2 and H_2O, but under certain conditions they accumulate in very great quantities in the body. The urine then contains some or all of these bodies in varying amounts.

The accumulation of these acids in the body constitutes the best known type of *acidosis.* The acidoses of diabetes, of starvation, of cholera, etc., are all characterized by the appearance of acetone bodies in the urine.

Though the occasions leading to their appearance are well known, and though fairly conclusive proof as to their source has been produced, the question of the nature of the defect that is responsible for their accumulation in the body is still undecided. It is known that this defect

is in some way often linked with the metabolism of carbohydrates. When carbohydrates are not ingested, or are not resorbed from the intestines, or when, as in diabetes, the body cannot utilize d-glucose, this defect appears in the metabolism of fat, resulting in accumulation of the acetone bodies (See Fat Metabolism, Part XIII).

(*b*) *Excretion of Acetone Bodies*

In milder cases of acidosis, only acetone may be found in the urine, but in the more severe cases all three of the acetone bodies are excreted. The amounts eliminated are proportionate to the degree of acidosis. This fact lends great clinical value to the tests for these bodies. Unfortunately the quantitative methods involved are not very suitable for clinical use. The acids, however, are excreted combined with ammonia, and by quantitative ammonia measurements we obtain an approximate idea of the degree of acidosis.

The actual amounts of the acetone bodies excreted may be very large. It is rare that the sum of the acetone and diacetic elimination surpasses 7 grams, but as much as 150 grams of β-oxybutyric acid may be found in the urine in severe diabetic acidosis.

(*c*) *Methods for the Determination of the Acetone Bodies in the Urine*

i. Qualitative Methods for the Detection of Acetone

1. Frommer's Test for Acetone

To 10 c.c. of urine about 1 gram of (solid) potassium hydrate is added. Before solution has occurred 10–12 drops of a 10 per cent solution of salicyl aldehyd in absolute alcohol are added and the mixture warmed to about 70° C. At the zone of contact of the alkali and urine an intense purplish red ring develops in the presence of acetone.

This test is specific for acetone (no reaction with diacetic acid); it is extremely delicate; and it may be performed without distilling the urine as must be done with the older tests. It is to be recommended for routine use. (Neuberg, Bohrisch, Webster).

2. Legal's Test for Acetone

To five c.c. of urine is added a small crystal of sodium nitroprussid. After solution has occurred (the urine should be cool) sodium or potassium hydrate is added in excess. A ruby red color appears, which fades rapidly to yellow. This color is given by both creatinin and acetone. Therefore, before the ruby red color has faded glacial acetic acid is added in excess. In the presence of acetone the red color will change to a purple or violet tint, while, with creatinin the red color will fade at once to a clear yellow or green.

This test is positive with diacetic acid. It will be positive with the untreated urine only when considerable amounts of acetone are present. To render the method more delicate the distillate from the urine should be used.

ii. Qualitative Methods for the Detection of Diacetic Acid (Aceto-acetic Acid)

The following two methods are the best ones to use in ordinary clinical work:

1. Arnold's Test for Diacetic Acid

REAGENTS.—Two solutions are necessary:

SOLUTION I

Paramidoacetophenon	1 gram
Distilled water	100 c.c.
Hydrochloric acid (conc.)	about 2 c.c.

The paramidoacetophenon is dissolved in the water with constant shaking, and hydrochloric acid being added by drops till the yellow solution becomes water clear (no excess acid).

SOLUTION II

Sodium nitrite, 1 per cent aqueous solution.

TECHNIC.—To 10 c.c. of Solution I, 5 c.c. of Solution II, and 15 c.c. of urine are added. One or two drops of concentrated ammonium hydrate are now dropped in. A non-characteristic brownish red color appears. Add an excess of concentrated hydrochloric acid. If diacetic acid is present a beautiful purple color develops. In the absence of diacetic the red color changes to yellow on the addition of acid.

This test is not positive with acetone, with β-oxybutyric acid nor with drugs. It is on this account much to be preferred to Gerhardt's test.

2. Gerhardt's Test for Diacetic Acid

Ten per cent ferric chlorid solution is added drop by drop to 10 c.c. of urine until no further clouding is noted. The mixture is then filtered. A few drops more of the ferric chlorid solution are added to the filtrate. If diacetic acid is present the filtrate should now have a Bordeaux red color.

This color may, however, be due not to diacetic acid but to certain *drugs,* especially salicylic acid, aspirin, diuretin, salol, phenacetin, acetates and formates. If the solution be *boiled,* the red color due to diacetic will fade, while that due to all of the above mentioned drugs (except the last two) will persist.

iii. Qualitative Methods for the Detection of l-β-Oxybutyric Acid

Of the methods recommended for this purpose, that of Hart is the best. This test is not very delicate; but for clinical purposes it is very satisfactory.

1. Hart's Test for l-β-Oxybutyric Acid

To 20 c.c. of urine an equal amount of water is added and a few drops of acetic acid. The mixture is boiled down to about 10 c.c. in volume (to remove

acetone and diacetic). The volume is then again brought up to 20 c.c. with water, and 10 c.c. of the mixture is then placed in each of two test tubes. To one of these add 1 c.c. of hydrogen peroxid, warm gently, and allow to cool. Then add to each tube 0.5 c.c. of glacial acetic acid and a small crystal of sodium nitroprussid. Then layer 2 c.c. of conc. ammonium hydrate on the solution in each test tube; and allow the tubes to stand for four or five hours. If l-β-oxybutyric acid is present in the urine, the tube to which peroxid was added will show a purplish red contact ring; while in the control tube no purple color will be seen.

iv. Quantitative Determination of l-β-Oxybutyric Acid

The methods here advised are probably the best and simplest for our purposes.

1. Black's Method

One hundred c.c. of urine are faintly alkalinized with sodium carbonate and evaporated over the steam bath in a porcelain dish to about 10 c.c. This residue is then cooled, acidified with a few drops of hydrochloric acid and made into a thick paste with plaster of Paris. As soon as this mixture begins to set it is stirred and broken up with a strong glass stirring rod. The dry mass is then extracted with pure ether in a Soxhlet apparatus for two hours. The ether extract is then evaporated to dryness; the residue is dissolved in a small amount of water, and this aqueous solution is shaken up with bone black and filtered clear. Sufficient water is then added to bring the volume of the filtrate up to 25 c.c., when its rotation is determined with the polariscope. The 189.4 mm. tube should be used. Each degree on the scale is then the equivalent of 2.18 per cent of l-β-oxybutyric acid. The percentage thus determined must be divided by four to allow for the concentration of the urine from 100 c.c. to 25 c.c. before the polariscopic examination.

2. Shaffer's Method

Principle.—The acid is oxidized to acetone and CO_2 with potassium bichromate.

Technic.—25–250 c.c. urine, the amount depending upon its content in l-β-oxybutyric acids, is placed in a 500 c.c. flask and an excess of lead acetate and 10 c.c. conc. ammonia added; the flask is then filled to the mark with distilled water, the flask well shaken, and the contents filtered. Of this filtrate, 200 c.c. are diluted to 500 c.c., then 15 c.c. conc. H_2SO_4 added, and a little talcum (to prevent "knocking") and 250 c.c. are distilled over (= *distillate A*). As the distillation goes on, it is well to replace the water as it evaporates by means of a dropping funnel. This "distillate A" contains the preformed diacetic acid, that formed from acetone, along with volatile fatty acids. The residue is distilled with 400–600 c.c. of a 0.1–0.5 per cent solution of potassium bichromate, this solution also being allowed cautiously to run in from a dropping funnel as the distillation proceeds. About 500 c.c. of distillate is collected (=*distillate B*). To the latter is added 20 c.c. of a 3 per cent solution of H_2O_2, and the mixture distilled again; in this last distillate, the acetone is titrated in the ordinary way with iodin and thiosulphate.

If it be desired to know also the content in acetone bodies present as preformed acetone and diacetic acid, distillate A may be redistilled after the addition of 5 c.c. of 10 per cent NaOH (to fix the volatile fatty acids) and the distillate from it titrated with N/10-iodin solution and thiosulphate solution.

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7. Fats in the Urine (Lipuria; Chyluria)

In *tropical hematochyluria,* due to filariasis, the worms, wandering, create abnormal communications between the lymph vessels and the urinary passages. Fat, and sometimes fibrin, may then appear in the urine and give it a milky appearance. The cause of *non-parasitic chyluria* is unknown.

In certain other conditions (*phosphorus poisoning; chronic parenchymatous nephritis*), minute amounts of fat may appear in the urine (*lipuria*).

The fat may be visible to the naked eye and on microscopic examination. In chyluria, if the urine be made alkaline, and shaken with ether, the fat will dissolve in the ether and the urine will become clear.

Caution! Remember that urine may be contaminated by fat or oil used to lubricate a catheter.

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8. Ferments in the Urine

Ferments, including amylase (diastase), lipase, pepsin, and perhaps trypsin, have been found in the urine.

The determinations of *diastatic activity* are of some interest in connection with the study of renal function (*q. v.*). *Lipase* may appear in the urine in fat-necrosis of the pancreas and may then have diagnostic value.

(*a*) *Determination of Diastase in the Urine (Wohlgemuth's Method)*

Reagents.—A one per cent solution of Merck's, or Kahlbaum's, soluble starch is prepared by stirring the starch powder into a measured amount of cold distilled water and gradually heating until with constant stirring in about 15 minutes the solution is approximately clear. After cooling, the solution is poured into a suitable volumetric flask and made up to exactly the original volume. The starch solution should be filtered before use if starch particles still remain undissolved. It may be kept several days in an ice chest. If a slight precipitation occurs, the clear supernatant fluid should alone be used. If the precipitation is marked the starch solution must be discarded.

Technic.—Ten test tubes are numbered consecutively, and are each graduated at the 6 c.c. mark. Into each is then pipetted 5 c.c. of the starch solution. Two c.c. of urine are now accurately diluted with 6 c.c. of distilled water. With a pipet calibrated in hundredths of a c.c., the following amounts of diluted urine are delivered into the numbered tubes; 0.88 c.c.—0.72—0.56—0.40—0.32—0.24—0.16—0.08—0.00. The level of fluid in each tube is now brought up to the 6 c.c. mark with distilled water. One-half c.c. of toluol is then added to each to prevent bacterial action; and the tubes are corked and placed close together in the incubator at 37° C. for 24 hours. Then the tubes are removed and the ferment action checked by chilling the tubes in ice water. Each tube is then filled nearly to the top with cold water, and to each 3 drops of N/10-iodin solution are added and the tubes well shaken.

Where the starch has all been broken down to dextrin, maltose, etc., the tube remains yellow, but where the ferment action has not completely removed the starch, the blue color of the starch iodin reaction is seen. The first tube that shows no blue is selected, and from the known proportions of urine and starch solution in this tube, the number of c.c. of 1 per cent starch solution that would be split by 1 c.c. of urine is calculated. For instance, if the first tube that shows no blue contains 0.08 c.c. urine (equals 0.32 c.c. of diluted urine) and 5 c.c. (1 per cent) starch solution, then

$$.08 : 5 :: 1.0 : x \quad x=62.5$$

The result is expressed as follows: $D\ \frac{37°}{24h} = 62.5$. This means that the urine examined contained sufficient diastase (D) to convert 62.5 c.c. of 1 per cent starch solution to dextrin and sugar acting at 37° for 24 hours.

Wohlgemuth employs the urine obtained at the second voiding in the morning for examination. The diastase is greatest in the urine during fasting and decreases three to four hours after meals (see Renal Functional Tests, Part X).

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(*b*) *Determination of Lipase in the Urine (Kastle and Loevenhart)*

Place 5 c.c. urine in each of three flasks. Boil one to destroy any ferment present. In the second, determine the acidity by titration with N/10-NaOH, using phenolphthalein as the indicator. Add the same amount of N/10-NaOH required to neutralize this 5 c.c. of urine to each of the other two flasks. To each add, also, 0.25 c.c. ethylbutyrate and 0.1 c.c. toluol. Incubate all three flasks at 37° C. for 24 hours. Now add to each flask N/10-HCl in amounts exceeding by 0.5 c.c. the amount of N/10-NaOH previously added. Remove the butyric acid by shaking with 50 c.c. ether. Add the ether extract to 25 c.c. alcohol, which has been neutralized to phenolphthalein. The amount of butyric acid is then determined by titrating with N/20-KOH (alcoholic) (1 c.c.=0.0044 g. butyric acid).

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9. Ehrlich's Diazo-reaction in Urine

The substances in urine that yield this beautiful color reaction are unknown.

Reagents.—Two solutions may be kept on hand for making the reagent.

Solution I = 5 sulphanilic acid + 50 c.c. conc. HCl + 1000 c.c. H_2O.

Solution II = 0.5 g. sodium nitrite + 100 c.c. H_2O.

Just before using, add exactly 10 drops of Solution II to 25 c.c. of Solution I.

Technic.—To 4 c.c. of urine add an equal volume of the reagent and 1 c.c. of ammonia; shake. An intense red color (scarlet, carmine, orange red) appears, if the reaction be positive, and, on shaking, a red foam is obtained.

The reaction may be helpful in the diagnosis of typhoid fever, being positive in most cases, from the first week on. If the patient drinks much water it may be necessary to concentrate the urine to secure a positive reaction. The reaction may also be present in severe cases of measles, in pneumonia, in trichinosis, in sepsis, and in pulmonary or miliary tuberculosis. It is *not* positive in meningococcus infections, or

in acute rheumatism. The reaction is, in reality, of very little practical value.

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10. Drugs and Their Derivatives in Urine

Iodin and Bromin.—To 5 c.c. of urine, add fresh chlorin water, or fuming HNO_3, and extract with chloroform. *Iodin,* red; *bromin,* yellowish brown.

Lead in the Urine.—Concentrate 1–2 liters urine by evaporation to 1/5–1/10 its volume. Add 50 c.c. conc. HCl; warm on the water bath and add successively small quantities $KClO_3$ until decolorized to a bright yellow and no longer smells of chlorin. Filter hot and wash filter and funnel with hot water. Add sodium bicarbonate to the filtrate until the reaction is only feebly acid. Hydrogen sulphid is now run into the filtrate. If lead is present it will be precipitated as blackish lead sulphid. This precipitate is collected on a small filter, washed; then filter and precipitate placed in a beaker and dilute HNO_3 added and heated until solution of the lead sulphid has occurred. The solution is then diluted with water and filtered. The filtrate is evaporated to dryness and the residue redissolved in a small amount of water. This solution (lead nitrate) should give the reactions for lead; a black precipitate with H_2S; a white precipitate with weak sulphuric acid; yellow with potassium chromate and potassium iodid.

Arsenic.—Treat, as for lead with HCl and $KCLO_3$, to remove organic material, and apply Marsh's test (vide Manuals of Chemistry).

Mercury.—To the total 24 hour urine, add 10 c.c. conc. HCl and a little brass-wool or copper filings; heat to 50°–60° C. for one hour. Allow to stand 24 hours. The Hg forms an amalgam on the metal. Pour off the urine, wash the metal repeatedly with water containing a trace of KOH, then with alcohol and ether. Dry in the air. Place the dried metal in a long narrow thick-walled tube, sealed at one end (carefully cleaned and dried); heat the bottom of the tube to redness. The Hg volatilizes and becomes deposited on the cooler walls of the tube above. This, exposed to iodin vapor, turns red, due to the formation of crystalline HgI_2.

Carbolic Acid.—To 300 c.c. of urine add 20 c.c. of conc. sulphuric acid and distil the mixture (wire gauze) until about ¼ the amount has gone over into the distillate. If pathological amounts of phenol are present in the urine a small portion of this distillate will give the following reactions. It turns a bluish violet upon addition of a small amount of ferric chlorid solution; or upon the addition of bromin water, a yellow crystalline precipitate is formed.

Potassium Chlorate.—To 8 c.c. urine add 2 c.c. conc. HCl, and boil; a dark (greenish) discoloration occurs, often disappearing on further heating.

Salicylic Preparations.—With ferric chlorid solution, a red color appears. The presence of salicylates is often mistaken for diacetic acid. Antipyrin yields a similar reaction. The color does not fade on boiling; the color due to diacetic acid does fade.

Chloral Hydrate.—The urine reduces Fehling; it does not ferment; it is levorotary, owing to the presence of urochloralic acid (a conjugated glycuronic acid).

Acetanilid.—Boil 8 c.c. urine with 2 c.c. conc. HCl; cool; add 2–3 c.c. of 3 per cent solution of carbolic acid, and a drop of dilute solution of chromic acid. A red color appears, which turns blue on adding NH_4OH to alkalinity.

Phenacetin.—To 8 c.c. urine add 2 drops concentrated HCl, 2 drops 1 per cent solution of sodium nitrite, 5 drops alkaline aqueous solution of α-naphthol, and make alkaline with NaOH; a beautiful red color appears, turning violet if HCl be added.

Santonin.—The urine is yellow in color; on adding NaOH it turns scarlet; after a time, the color disappears.

Pyramidon.—The urine is often red; on addition of dilute (2 per cent) ferric chlorid solution, an amethyst color appears.

Phenolphthalein.—After use as a purgative, the urine turns purplish red, if it be made alkaline.

Urotropin.—Add bromine water to the urine; an orange yellow precipitate appears.

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11. Sediments in the Urine

The urinary sediment may be collected:

1. By allowing it to settle in the bottom of a conical glass by standing, undisturbed, for 12–14 hours.

2. Quickly, by means of a centrifuge.

The first method should be avoided whenever possible. For examination of urinary sediment a *perfectly fresh* specimen is very much to be preferred. The more important features of the examination are *organized sediments,* which are especially liable to deteriorate, or to disappear, upon standing. It is good practice always to centrifugalize the well-mixed fresh specimen for the same length of time at the same speed to obtain a rough quantitative estimate of the abundance of the sediment in routine examinations. A marked haziness persisting after centrifugalization is due to bacteria.

A drop of the sediment is taken up with a pipet from the bottom of the centrifuge tube, placed upon a clean glass slide and covered with a cover slip. The low power of the microscope should be used first, with the illumination reduced so as to bring out the outlines of objects studied. Details of blood cells, casts, etc., occasionally require the use of a higher power lens.

Sediments may consist of *formed elements*—so-called *"organized sediments";* including red and white blood corpuscles, epithelial cells (vesical, renal), casts, tissue fragments, spermatozoa, animal parasites or bacteria. Or, they may consist of *amorphous* or *crystalline precipitates* (*"unorganized sediments"*).

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(*a*) *Organized Sediments in the Urine*

i. Red Blood Corpuscles

These may be seen as normal intact red cells, in the form of yellow disks, or, when lying on edge, of biscuit-shaped structures. In some urines, the cells may be swollen, or laking may have occurred ("shadows"). In concentrated urines (especially when urine is evaporating on a glass slide), "thorn-apple" forms appear (see Hematuria).

ii. White Blood Corpuscles (including "Pus Cells")

In acid urine, these appear as round, pale, colorless structures, tolerably refractile, and usually a little larger than red cells. They may be easily confused with epithelial cells, but the "glycogen-reaction" quickly

distinguishes them, since with Lugol's solution the white blood cells stain mahogany-brown, epithelial cells only yellowish. Moreover, the character of the nuclei (usually polymorphonuclear), clearly revealed by the addition of dilute acetic acid, also differentiates them.

Normal urines contain an occasional leukocyte. Larger numbers point to inflammations (urethra, bladder, ureter, renal pelvis, kidney). They are sometimes attached to casts (leukocyte casts). Pus in the urine (*pyuria*) consists essentially of masses of leukocytes. Usually, large numbers of bacteria (pyogenic cocci, gonococci, colon bacilli) are also present. The pus cells easily undergo change, fusing to a sticky mass in which only here and there nuclei may be present, the outlines of the cells having disappeared. Certain chemical tests are here helpful.

Donne's Pus Test.—Treat the sediment with KOH and stir; a sticky mass appears, which can be drawn out into threads with a glass rod. Mucus, on the contrary, is converted into a thin fluid containing flocculi.

Vitali's Pus Test.—Place some of the sediment in a test tube; acidify with acetic acid; on the surface, float a few c.c. of guaiac tincture; after a short time, if pus be present in considerable quantity, a blue color will appear.

iii. Mucus-Nubecula

The "nubecula" of normal urine is due to *mucus*. In sediments under the microscope, mucus usually appears as a transparent mass, in which cells are embedded. Often, the mucus appears as bands or threads, more or less resembling hyaline casts; these bands are called *false casts*. They are usually broader and longer than casts and are often branched. Unlike casts, they do not dissolve in acetic acid or in alkalis. The *shreds* in the urine, after a preceding gonorrheal infection, consist of mucus, derived from the mucous secretions of the prostate and of Cowper's and Littré's glands; they may be stained with methylene blue when gonococci can frequently be seen in them, though by no means always.

iv. Fibrin

This is easily recognized under the microscope as a fine network, or as delicate threads.

v. Epithelial Cells

In males, these are usually derived from the urinary passages, occasionally from the kidneys. In women, however, the urine commonly contains large numbers of flat epithelial cells from the labia and vagina.

In general, renal epithelial cells are round or cubical and possess distinct, relatively large, nuclei in a protoplasm, often fatty; epithelium from the urinary passages is more usually cylindrical or squamous.

The superficial epithelium of the urinary passages is flat, polygonal; the cells in the deeper layers are rounded and often have a pear-shaped process. Attempts sharply to distinguish, by their form, those coming from the pelvis of the kidney from those coming from the bladder are futile.

The epithelium of the male urethra is cylindrical; cells of this type are often mixed with pus cells and gonococci in a gonorrheal discharge.

vi. Casts or Urinary Cylinders

These are masses of material, deriving their cylindrical shape from the urinary tubules in which they are molded. They are present in the urine (*cylindruria*) in most nephropathies, being very numerous in the acute nephropathies, and in the chronic nephropathies with renal edema, less numerous in the nephropathies associated with contraction of the kidneys. They are also present in the urine in chronic passive congestion (stasis-kidney), in febrile albuminuria and in jaundice (stained yellow). In acidosis with threatened diabetic coma, "showers" of short granular casts (*coma casts*) may appear. "Showers" of hyaline and, sometimes, of granular casts occur in exacerbations of renal disease.

Several varieties of casts occur: (a) hyaline, (b) granular, (c) waxy, (d) epithelial, (e) fatty, (f) blood cell casts, (g) hemoglobin casts, and (h) leukocyte casts.

Hyaline Casts.—Pale, transparent, homogeneous casts, with delicate contours, and rounded ends (often hard to make out). The commonest form of cast, indicating the existence of a nephropathy, but throwing no light on the variety of nephropathy. Some of the so-called *cylindroids* are probably hyaline casts with pointed ends, while others are "false casts," composed of mucus.

Granular Casts.—Similar to (a) but the substance is finely granular, usually rather short and plump, often yellowish. The granules may be coarse or fine; they are soluble in acetic acid. One sees various transitions to epithelial casts. Granular casts are met with chiefly in the inflammatory and degenerative nephropathies.

Waxy Casts.—Yellow, highly refractive casts, with clean-cut contours, and often exhibiting irregular curves, notches and fractures; rare except in severer forms of chronic renal disease.

Epithelial Casts.—Aggregations of renal epithelium, sometimes preserving their original arrangement in the tubules ("epithelial tubes"). The cells are often filled with granules or fat droplets, or there may be a homogenous necrosis. We distinguish these casts consisting of epithelium from the hyaline and granular casts with a few epithelial cells upon their surface.

Fatty Casts.—Made up of masses of fat droplets, often arranged in

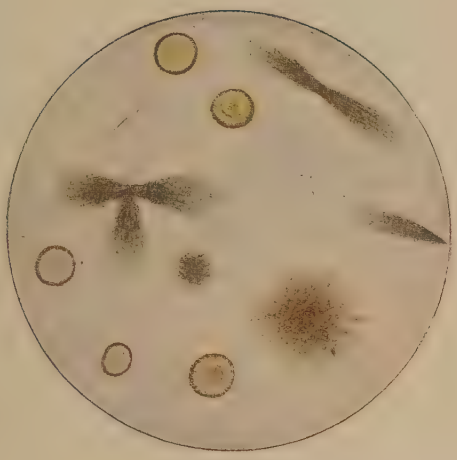

Fig. 1.—Tyrosin and Leucin. (After H. Rieder, "Atlas d. klin. Mikroskopie d. Harnes," published by F. C. W. Vogel, Leipzig.)

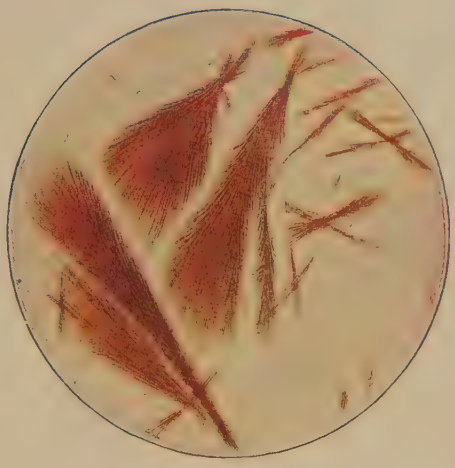

Fig. 2.—Phenylglucosazone Crystals. (After N. v. Jagic u. H. K. Barrenschen, "Atlas u. Grund. d. Klin. d. Mikroskopie," published by M. Perles, Wien.)

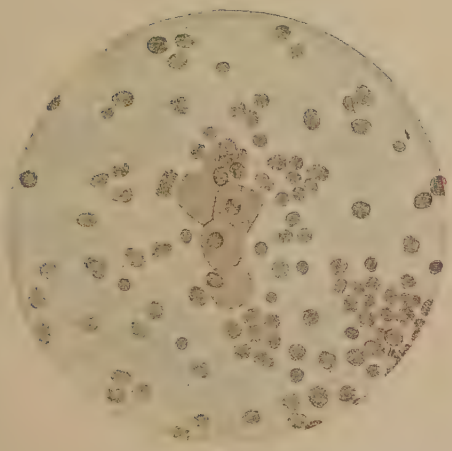

Fig. 3.—Blood and Pus from Urine. (After N. v. Jagic u. H. K. Barrenschen, "Atlas u. Grund. d. Klin. d. Mikroskopie," published by M. Perles, Wien.)

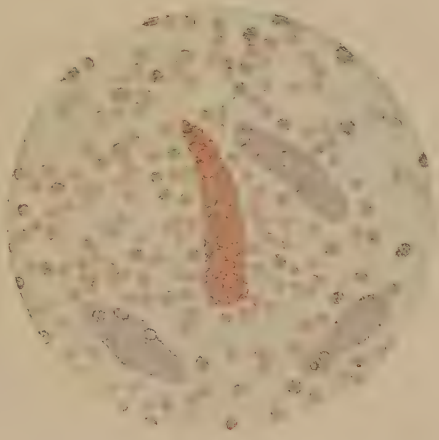

Fig. 4.—Sediment from Urine in Hemorrhagic Nephritis. (After N. v. Jagic u. H. K. Barrenschen, "Atlas u. Grund. d. Klin. d. Mikroskopie," published by M. Perles, Wien.)

groups corresponding to renal epithelial cells. They are probably remains of true epithelial casts.

Blood Cell Casts.—Red cells in masses, molded by the renal tubules. The blood comes from the glomeruli (hemorrhagic glomerulonephritis).

Hemoglobin Casts.—Made up of brown granules of Hb. They are found in hemoglobinuria due to $KClO_3$ poisoning, in paroxysmal hemoglobinuria, etc.

Leukocyte Casts (Pus Casts).—Cellular casts; the single cells are seen to have polymorphous nuclei on adding acetic acid. Most common in pyelonephritis.

vii. Tissue Fragments

Bits of mucous membrane may be shed and passed with the urine (acute cystitis). Fragments of a papilloma or of a carcinoma may be found, and may be studied histologically.

Fig. 439.—Ovum of Schistosoma hematobium.

viii. Spermatozoa

These are present in normal urine after coitus or onanism. They may also be present in the different forms of spermatorrhea. The form is characteristic.

ix. Animal Parasites

It is rare to find animal parasites in the urine in temperate climates, more common in the tropics. Among those that occur may be mentioned (a) *Amebae;* (b) *Echinococcus* (hooks, membranes); (c) *Filarial larvae* (tropical hematuria and chyluria); (d) eggs of the human blood fluke *Schistosoma hematobium* (Bilharziosis or Egyptian hematuria); (e) *Oxyuris* or *pinworm*, occasionally (in young girls) wanders through the urethra into the bladder; (f) *trichomonas vaginalis* (of no import).

x. Vegetable Parasites and Bacteria

These are of no importance when seen in urine unless they are found in a specimen obtained by aseptic catheterization.

In **bacteriuria,** the urine is usually turbid, especially if the bacteria

are motile. It may be impossible to make such urines clear by centrifugalization. The bacteria may be studied by *microscopic examination* (fresh drop, smear), by *cultural methods,* or by *animal inoculation.*

Among the *non-pathogenic bacteria* that may be present are: (a) micrococcus ureae; (b) bacterium ureae; (c) urinary sarcina; (d) several non-pathogenic streptococci; and (e) bacillus cystiformis (Clado).

Among the *pathogenic bacteria* occurring in urine are:

Bacillus tuberculosis.—The finding of the tubercle bacillus in the urine is of the greatest clinical significance. It occurs both in cases of generalized tuberculosis (as a result of bacillemia) and more particularly in cases of tuberculosis of the genito-urinary organs. In this last case it is usually associated with a pyuria and frequently with a hematuria.

In searching for tubercle bacilli in the urine it is of especial importance to obtain an uncontaminated specimen since the smegma bacillus may readily lead to confusion (see Part X).

The sediment from about 50 c.c. of thoroughly centrifugalized urine should be used. If much pus is present antiformin treatment of the sediment may be advisable. In all doubtful cases inoculation of a guinea-pig should be resorted to.

Gonococcus.—Of great diagnostic importance. Intracellular, biscuit-shaped, diplococci, best seen in smears stained with methylene blue. They decolorize by Gram.

Bacillus coli.—Of considerable diagnostic importance. (Cystitis; pyelitis).

Bacillus typhosus.—Of importance for prophylaxis (*bacillus carrier*!), and also for diagnosis in the rare cases of pyonephrosis due to the typhoid bacillus. Throughout the course of typhoid fever, after the first week, typhoid bacilli are often demonstrable in the urine.

Pyogenic cocci.—Rare as a cause of cystitis and pyelitis. Streptococci not uncommon in acute nephritis. Staphylococci occasionally in general sepsis (adolescence).

xi. Artefacts

Urinary sediments may be accidentally contaminated by foreign bodies of various sorts; *e. g., starch granules, cotton fibers, linen fibers, silk fibers, wool,* etc.

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Fig. 440.—Contaminations of Urinary Sediment: (a) Feather Particles, High and Low Magnification; (b) Fragments of Pubic Hair; (c) Starch Granules from Flour (Wheat); (d) Fat Droplets, High Power; (e) Cotton Threads; (f) Wool Threads, Colored and Natural; (g) Silk Fibers; (h) Flax Fibers, Natural and Washed; (i) Collected Fibers Under Low and High Power. (After H. Rieder, "Atlas d. klin. Mikrosk. d. Harnes," published by F. C. W. Vogel, Leipzig.)

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(*b*) *Non-organized Sediments in the Urine*

Here, in addition to microscopic examination, chemical and, especially, microchemical tests may be very helpful in differentiation.

Some of the more characteristic reactions are given in the accompanying table (*after Spaeth*); they can be made in a test tube, or under a coverslip on a glass-slide (microchemical tests).

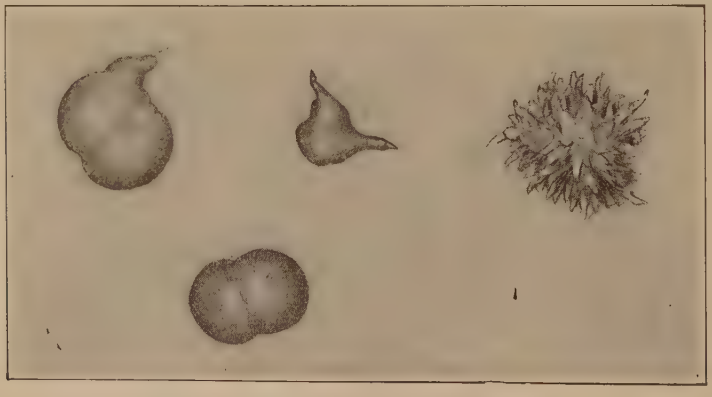

Fig. 441.—Ammonium Biurate Crystals.

TABLE FOR QUICK CHEMICAL ORIENTATION WHEN STUDYING NON-ORGANIZED SEDIMENTS

Warm the sediment with water to 50° C.	
It dissolves easily = urates It dissolves with great difficulty = $CaSO_4$	It is insoluble: Phosphates and carbonates of Ca and Mg, triple phosphates, ammonium urate, calcium oxalate, calcium sulphate, cystin, xanthin, tyrosin.
If insoluble, warm with a few drops strong acetic acid:	
The following dissolve: 1. Phosphates (no gas evolved). 2. Carbonates (gas evolved). 3. Triple phosphate. 4. Ammonium urate after standing 15 minutes (crystals of uric acid separate out).	The following remain undissolved: Uric acid, calcium oxalate, calcium sulphate (dissolves in much water), xanthin, cystin, tyrosin, organized sediment.
If not dissolved, heat with HCl:	
The following dissolve: Oxalate of lime, xanthin, cystin, tyrosin, leucin. Tyrosin, xanthin and cystin are soluble in ammonia.	The following remain undissolved: Uric acid; organized sediments.

Fig. 442.—Ammonium Magnesium Phosphate Crystals. (Triple Phosphates.)

Non-organized sediments may be further classified according as they occur in *acid* or in *alkaline* urine. In *amphoteric* urine, sediments belonging to either of these classes may be found. In the following table, prepared by Dr. Sydney R. Miller, for convenience of consultation, the main points are given.

Reaction of Urine	Crystals	Shape	Color	Heat	Acetic Acid	HCl	NH^4OH	KOH	Remarks
Acid	Amorph. Urates	None	Pink	Soluble	Soluble	Soluble	Soluble	Soluble	Murexid test. Yield uric acid crystals.
	Uric Acid	Rosettes Sheaves Whetstone	Yellow to Brown	Insoluble	Insoluble	Insoluble	Insoluble	Soluble	Murexid test.
	Calcium Oxalate	Refractile Octahedra	White	Insoluble	Insoluble	Soluble	Insoluble	Insoluble	Dumb - bell forms occur.
	Calcium Sulphate	Clusters of thin tablets or needles	White	Insoluble	Insoluble	Soluble with difficulty	Insoluble	Insoluble	Soluble c̄ hot H_2O. Test c̄ $BaCl_2$.
Neutral	Di-calcium Phosphate	Wedges Prisms	White	Insoluble	Soluble	Soluble	Insoluble	Insoluble	Rare. Soluble in 20 per cent $(NH_4)_2SO_4$.
	Ammonium Biurate	Thorn-apples Dumb-bells	Gray Brown	Insoluble	Soluble	Soluble	Insoluble	Soluble	Yield uric acid crystals. c̄ acids.
Alkaline	Amorph. Phosphate	None	Gray Brown	Insoluble	Soluble	Soluble	Insoluble	Insoluble	
	Amorph. Carbonate	None	Gray Brown	Insoluble	Soluble CO_2 evolved	Soluble CO_2 +	Insoluble	Insoluble	
	Triple Phosphate	Coffin-lids "×" forms	White	Insoluble	Soluble	Soluble	Insoluble	Insoluble	Insoluble in 20 per cent $(NH_4)_2SO_4$.
	Calcium Carbonate	Dumb-bells	White	Insoluble	Soluble CO_2 evolved	Soluble CO_2 +	Insoluble	Insoluble	

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12. Urinary Calculi

These may be composed of *organic* substances (uric acid, ammonium urate, xanthin or cystin), or of *inorganic* substances (phosphates, carbonates or oxalates of lime, magnesia, sodium, potassium or ammonium). The organic stones burn completely on incineration on platinum, inorganic stones do not. For simple analytical methods, the following table will usually suffice:

Chemical Analysis of Urinary Calculi

Murexid test	with ammonia — purple red with KOH — purple violet	= uric acid = urates
Murexid test	with ammonia — yellow and with KOH — orange yellow	= xanthin
The powder burns with a feebly illuminant blue flame, yielding odors resembling burning sulphur, fat or asafetida.		= cystin
The powder effervesces with HCl		= calcium carbonate
The powder does not effervesce with HCl	but does so after incineration	= calcium oxalate
	even, after incineration	= earthy phosphates

Urate, phosphate and oxalate stones are common; other varieties are rare.

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Part X

Diagnosis of Diseases of the Urogenital Apparatus

Section I

METHODS OF EXAMINATION

The urogenital apparatus includes (A) the *uropoietic organs,* including the kidneys, the ureters and the urinary bladder, and (B) the *genital organs,* including in the *male,* the testes, the seminal vesicles, the spermatic cords, the prostate, the bulbo-urethral glands of Cowper, and the external genitals (penis, male urethra and scrotum), and, in the *female,* the ovary, the uterine tubes (or fallopian tubes), the uterus, the vagina, the epoöphoron and the paroöphoron, and the external genitals (the vulva, the vestibular glands of Bartholin, the clitoris, and the female urethra).

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A. General Remarks on the Examination of the Uropoietic System

This includes the *examination of the uropoietic organs* above mentioned, and the *examination of the urine.* The latter has already been discussed in Part IX.

1. Anatomical Structures

Uropoietic Organs.—The uropoietic organs (*organa uropoëtica*) include (1) the kidney (*ren*) on each side, (2) the corresponding *ureter,* and (3) the urinary bladder (*vesica urinaria*). The bladder is emptied in each sex through the *urethra,* a tube which, in the male (*urethra virilis*), serves also the genital function, though in the female (*urethra muliebris*) this tube is not concerned in the genital function.

Kidneys.—Each *kidney* presents an upper extremity and a lower extremity, an anterior surface and a posterior surface, and a lateral margin and a medial margin, the latter corresponding to the position of the *renal hilus* and the *renal sinus.* The kidney is enclosed in a fatty capsule (*capsula adiposa*). The surface of the kidney within the capsule is enclosed in two membranes, (1) a fibrous coat (*tunica fibrosa*), and (2) a coat of smooth muscle (*tunica muscularis*). The *functional* units of the kidney are the renal tubules (*tubuli renales*). The renal tubules are very complex structures, each tubule being divisible into several parts. The parts known as the convoluted renal tubules (*tubuli renales contorti*) are concerned chiefly with secretion; the parts known as the straight renal tubules (*tubuli renales recti*) chiefly with conduction. On examining a longitudinal section through a kidney, it is seen to be composed of a cortex (*substantia corticalis*) and a medulla (*substantia medullaris*). In the adult, traces of the fetal lobation are sometimes still visible, for each kidney is made up of several lobes (*lobi renales*), corresponding to the several renal pyramids (*pyramides renale*) of the medullary substance. The apices of these pyramids (*papillae renale*) project into the *renal calyces* of the pelvis of the kidney (*pelvis renalis*); here the straight tubules empty themselves through the foramina papillaria, the *area cribrosa.* The base of each pyramid (*basis pyramidis*) is situated at the junction of the medulla with the cortex; little bundles of straight tubules run out into the cortex so that in the cortex each lobe of the kidney is made up of a number of lobules (*lobuli corticales*), each lobule having a central core of straight tubules (*pars radiata* or *processus Ferreini*) and a periphery of convoluted tubules (*pars convoluta*). At the beginning of each renal tubule is one of the renal corpuscles (*corpuscula renis*) of Malpighi, made up of a tuft of blood vessels (*glomerulus*), and an epithelial capsule (*capsule glomeruli*). The renal arteries (*Aa. renis*) give off interlobar branches (*Aa. interlobares renis*), which in turn form the renal arches (*Aa. arciformes*) at the junction of medulla and cortex. These renal arches give off interlobular arteries (*Aa. interlobulares*) to the cortex, and straight arterioles to the medulla (*arteriolae rectae*). Each interlobular artery gives off small arteries (*vas afferens*) to a glomerulus; in the glomerulus, which is a rete mirabile, the vas afferens breaks up into glomerular capillaries; the blood passing through the latter comes out of the glomerulus through the efferent artery of the glomerulus (*vas efferens*), and this, in turn, breaks up into capillaries among the renal tubules. Thus the arterial blood reaching the cortex of the kidney passes through the glomeruli before being distributed to the renal tubules, a fact doubtless of fundamental importance for the physiology of the kidney.

Renal Pelves and Ureters.—The pelvis of the kidney (*pelvis renalis*) consists of a main reservoir and of a number of sacs (*calyces renales*). The renal pelvis is drained by the *ureter,* which consists of an abdominal part (*pars abdominalis*) and a pelvic part (*pars pelvina*). The wall of the ureter consists of an external fibrous coat (*tunica adventitia*), a middle muscular coat (*tunica muscularis*), and an internal mucous membrane (*tunica mucosa*). At its lower extremity, each ureter opens into the urinary bladder. Each ureter exhibits, normally, *three narrowings* of its lumen, (1) immediately below the beginning of the ureter,

(2) at the point where the ureter crosses the iliac vessels, and (3) at the lower end of the ureter; at any of these three natural constrictions of the ureter a calculus may lodge on its way from the renal pelvis to the urinary bladder.

Urinary Bladder.—The urinary bladder (*vesica urinaria*) lies behind and below the symphysis pubis in front of the rectum, in the male, in front of the vagina,

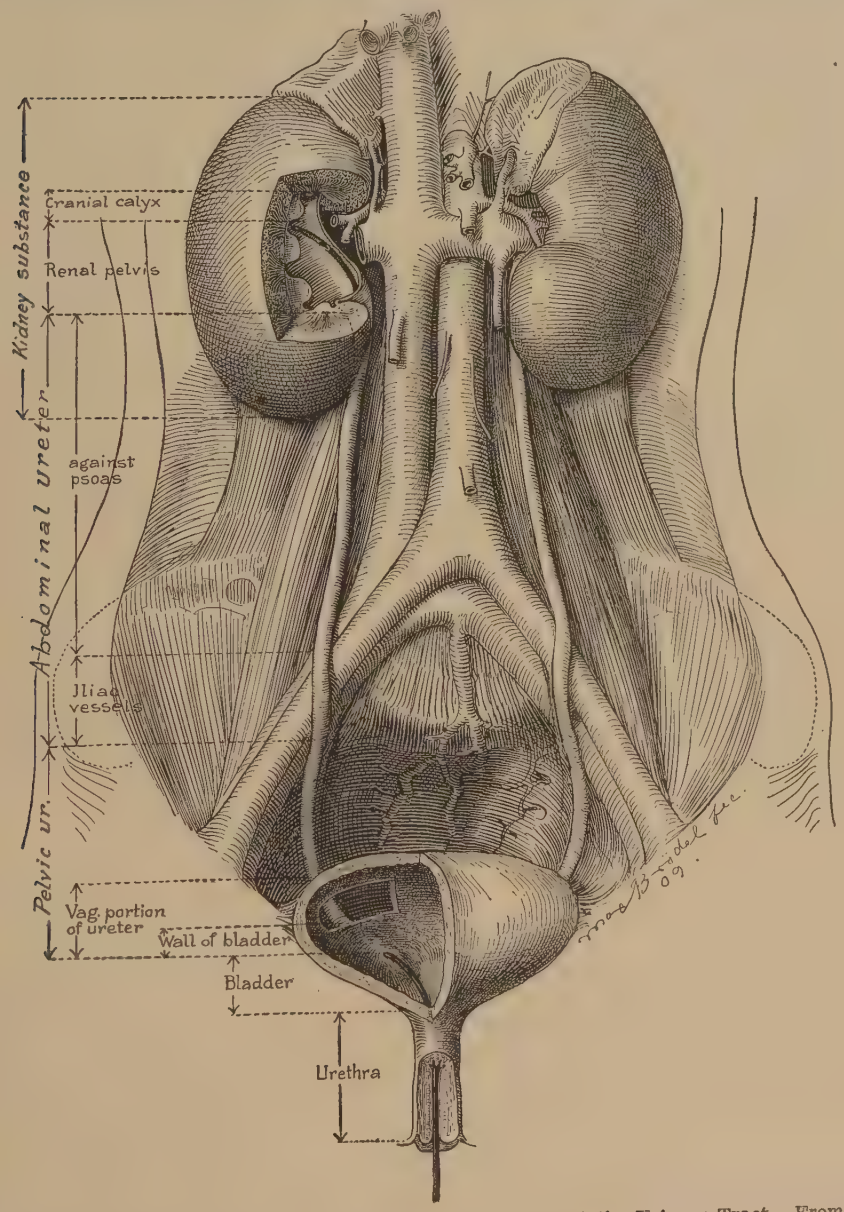

Fig. 443.—A Convenient, Practical Division of the Regions of the Urinary Tract. From the External Urethral Orifice to the Upper Calyx of the Kidney, as Traversed by a Renal Catheter. (After H. A. Kelly and C. F. Burnam.)

in the female. The involuted *urachus* extends from it to the umbilicus. The bladder is covered externally in part by peritoneum (*tunica serosa*), and its wall is made up from without inward of three coats, a muscular coat (*tunica muscularis*) which gives the bladder its power to expel the urine when the vesical sphincter is relaxed, a submucous coat (*tela submucosa*), and a mucous membrane (*tunica mucosa*) covered by laminated squamous epithelium. The bladder empties below at the internal orifice of the urethra (*orificium urethrae internum*) into the urethra. At the posterior inferior part of the bladder on each side is the opening of a ureter (*orificium ureteris*). The triangle at the base of the bladder enclosed by lines joining the orifice of the urethra with the orifices of the ureters, as sides, and by a line joining the orifices of the two ureters, as base, is known as the trigone (*trigonum vesicae of Lieutaud*). The nerve supply of the bladder will be described in Part XII.

2. Notes on the Physiology of Urinary Excretion

The main function of the kidney is to *excrete urine.* It may, in addition, possess a *function of internal secretion,* though concerning the latter, if it exist, but little is yet known.

Renal Excretion.—As an *excretory organ,* the kidney is certainly of very great importance to the body. Waste products of the body metabolism are, as is well-known, excreted chiefly through the urine and through the feces; to a less extent through the skin, the breath, and the saliva. These waste products consist of nitrogenous substances (urea, uric acid, amino-acids, ammonia) and non-nitrogenous substances (salts and water).

During excretion, the kidneys act partly as *filters,* partly as specific *secreting glands,* the production of the urine depending upon the coördinated activity of (1) the blood pressure, (2) the epithelial cells of the renal tubules, and (3) the osmotic influences between the blood and the urine (with the capillary wall between them), in the glomerulus, and between the lymph outside the blood vessels and the urine (with the epithelial cells between them) in the renal tubules.

The functions of the kidney, viewed as a semipermeable membrane between the blood and the urine, have been especially emphasized by Martin H. Fischer. His publications on edema and on nephritis are worthy of careful attention.

Calculations made from serial sections, and measurements of the kidney by Max Broedel, give us some idea of the *total number of tubules and glomeruli* in the normal kidneys. According to this investigator, there are approximately 4,000,000 tubules and glomeruli in the two kidneys. Were these tubules to be placed end to end, they would, he tells us, aggregate about seventy-five miles in length. If this calculation be correct, each tubule would secrete only between 8 and 10 c.c. of urine in a whole lifetime of seventy years.

Functions of Glomeruli and Tubules.—There has been much discussion as to the respective functions of the *glomeruli* and the *renal tubules.* At present, opinion supports the view that ordinarily water and some of

the salts (sulphates, phosphates, carbonates) are excreted by the glomeruli, and that the tubules excrete urea, uric acid, and, perhaps, sodium chlorid, while they absorb some of the water which has passed out through the glomeruli. In pathological states, foreign substances like sugar, peptones, albumin and hemoglobin are excreted chiefly by the glomeruli, while pigments and many poisons (*e. g.*, phloridzin, cantharidin) are excreted by the renal tubules. That these rules do not hold rigidly, however, is shown by other facts; thus, the tubules can excrete sugar in phloridzin poisoning, and, under certain circumstances, water and salts may be excreted by the epithelium of the renal tubules. It would seem as though the glomeruli and the renal tubules could, to a certain extent, take up one another's work.

According to Brodie, the glomerulus is a *propulsor;* by its quick expansion, it drives water out of the capsule, a function separate from its secretory activity. It seems probable that the glomerular epithelium has some selective power, and that the glomerulus is therefore not a mere filter.

Water-Excretion.—The *excretion of water* is, normally, chiefly a glomerular function, depending upon the rapidity of flow through its vessels, and, to a certain extent, upon the blood pressure, a certain minimal blood pressure being necessary for the excretion. Vasomotor influences must, obviously, play a very important part. When the minimal blood pressure falls below the level requisite for glomerular excretion of water, some water can be excreted through the tubular epithelium.

Excretion of Solids.—The *solids of the urine*, chiefly end-products of metabolism, are, for the most part, excreted through the renal tubules, though the excretion of solids by the glomeruli also occurs. When solids are excreted through the renal tubules, they must pass first through the endothelium of the capillary walls into the lymph; from the lymph they must pass through the epithelium of the renal tubule into the lumen of the tubule. Specific selective processes and non-specific osmotic processes both play a part. In the renal epithelium, important changes may take place in the substances which reach the cells; thus, we know that hippuric acid is synthesized in the renal epithelial cells, and that creatin is there converted into creatinin. These processes, of synthesis on the one hand, and of analysis on the other, are apparently carried on under the influence of enzymes.

When solids are excreted through the glomeruli, they have to pass through the endothelium of the glomerular capillaries, and then through the epithelium of the capsule of the glomerulus before reaching the capillary space and the renal tubule. The process is probably complex (filtration, selection, osmosis).

The complex structure of the renal tubules makes it probable that the *excretion of particular solids* may be functions of specific portions of the tubule. At any rate, we now know that a pathological kidney may lose

its capacity to excrete one solid, while retaining its power to excrete other solids; indeed, the recent studies teach us that, in disease, *it is necessary to consider the secretion of individual solids each for itself.* This fact will make one rather suspicious of so-called functional tests of renal secretion which are supposed to permit one to draw conclusions regarding the kidney as a whole from the mode of excretion of any single chemical substance.

Internal Secretion.—The idea that the kidney possesses also a function of *internal secretion* is based largely upon the fact that when animals are nephrectomized, life can be continued a little longer than otherwise by administering the expressed juice of kidneys removed from another animal of the same species.

3. Pathological Physiology of the Kidney

Blood Supply.—It has been pointed out above that the blood entering the cortex of the kidney passes directly to the glomeruli, and goes through them, before becoming distributed to the tubules. This arrangement has been compared with that of a compound engine, since the blood goes first to the high pressure glomerulus, in the same way as the steam goes to the high pressure cylinder, and afterwards passes on to the low pressure tubular capillaries, just as the steam, after losing much of its expansive force, goes to the low pressure cylinder of the engine, an arrangement that possesses marked mechanical advantages. It is obvious, therefore, that the capillaries of the glomeruli are subject to the greatest strain, first, in the way of higher pressure, and, second, because of the greater concentration of the substances to be excreted.

Damaged Tubules.—The secreting portions of the renal tubules, aside from the glomerular epithelium, seem to consist chiefly of the convoluted tubules and of Henle's loops. It is the convoluted tubules which, especially in intoxications, show degenerative change. When this degenerative change is slight (cloudy swelling), the tubules recover completely when the intoxication passes off. If the degeneration be more marked (granular, fatty, hyaline), the recovery may be less complete. In severe intoxications, actual necrosis of the renal epithelium occurs, and large masses of dead epithelium may be shed. Even when the renal epithelial cells are not killed outright, they may be so injured that portions of them are given off into the lumen, with formation of hyaline and granular casts. When the renal epithelium is desquamated, epithelial casts are formed. Blood casts are due chiefly to hemorrhages from rupture of glomerular capillaries in infectious processes.

Regeneration.—Even in health, a certain number of renal epithelial cells are destroyed, but the renal epithelium possesses a considerable capacity for *regeneration.* Even after extensive necrosis of these cells, as in the kidney of pregnancy, and in experimental intoxications with poisons which act especially upon the renal tubules, practically complete recovery may follow through regeneration of the renal epithelium (or so-called parenchyma), but it may also involve, and practically always does, to a certain extent, involve, the connective tissue (or interstitial tissue) of the kidney.

Dr. John McCrae forcibly illustrates this by comparing "the parenchymatous cell with the 'professional man' in a community, specially trained, not to be replaced but by one of his own class, impressionable by even slight external stimuli, not prone to be physically hardy, not overgiven to reproduction. The supportive

cell, on the other hand, is its 'laboring-class' brother, not trained in any high special task, whose supportive work can be replaced by any kind of tissue, even scar tissue, not readily impressionable, even by powerful, external stimuli, physically strong, and ready in reproduction. These two cells lie side by side in the kidney, exposed to the same toxic influences, but reacting to them each in its own way. A toxin strong enough seriously to damage the high-class cell is only strong enough to irritate the low-class cell to reproduction. When the high-class cell is killed by toxin, in the absence of regeneration by the remaining tubular cells, it leaves no one of its kind in its stead, and its place is occupied, but its function is not performed, by the progeny of its laboring-class brother."

Intoxications.—The *poisons* which reach the kidney consist largely of the end-products of metabolism (see Normal Composition of the Urine). In pathological states, an excess of these normal end-products may reach the kidney, or poisonous substances not present normally may arrive there. Among such abnormal poisons may be mentioned: (1) the toxic substances of infective processes, (2) the products of hemolysis, (3) the products of abnormal cell catabolism, and (4) various exogenous poisons taken in with the food or absorbed from the alimentary canal as a result of abnormal infectious, putrefactive, or enzymatic processes going on there.

Wear and Tear.—With *age,* the human kidney undergoes retrogressive changes, partly directly as a result of wear and tear of its constituent secreting structures, partly indirectly as a result of change in its arterioles. Thus through arteriosclerosis, the circulation in the kidney becomes markedly altered. The velocity of the blood-flow, its continuity, and the height of the blood pressure are all altered. Glomerulus after glomerulus becomes hyaline, atrophic, and fibrosed. Remaining glomeruli may, it is true, undergo hypertrophy, and to a certain extent compensate for those that are lost. The heart, in time, hypertrophies, and, by maintaining a higher minimal blood pressure, helps to keep up the urinary excretion. But a vicious circle is established. The kidney, already impaired, has to bear an ever-increasing load, and responds by (1) a gradual degeneration of its parenchyma and (2) a gradual increase in its interstitial tissue.

Diet.—The effect of *diet* upon the renal function has been much discussed. As we shall see in Part XIII, the end-products of protein metabolism and of nucleic-acid metabolism are largely excreted through the urine. In addition, the kidneys excrete a large part of the excess of water and of mineral substances from the body. The end-products of carbohydrate and fat metabolism are, however, excreted largely through the breath, though water and carbonates are also excreted through the kidney. The extractives of meats and soups are excreted through the kidney. Condiments, like mustard and pepper, and certain drugs (turpentine, copaiba, cantharides, salicylates, mercury, carbolic acid, lead, etc.) are believed to impose extra work upon the kidney and to be especially injurious to it.

When a kidney is diseased, or when extra work is thrown upon the kidneys as a result of disease elsewhere in the body, the effects of diet upon the kidney should be carefully considered, and the dietary so arranged that this important excretory organ shall be compelled to bear as little strain as possible.

When edema from any cause exists, it may be necessary to restrict both water and sodium chlorid in the diet. When the secretory function of the kidney is seriously impaired, and there is oliguria or complete anuria, it may be necessary temporarily to withhold food, except perhaps soluble carbohydrate, and to avoid the giving of drugs which can be harmful to the renal epithelium. In cases where the kidney, though fairly active, is somewhat insufficient, the tasks thrown upon it should be limited by restricting somewhat the protein intake, and avoiding food rich in extractives, and condiments. This is why short periods of milk diet are often beneficial in chronic renal disease.

Vicarious Elimination.—In renal insufficiency, in both human beings and experimental animals, a considerable degree of *vicarious elimination* can occur through the sweat, and through the feces. The studies of Plaggemeyer and Marshall have recently taught us much concerning elimination through the sweat. These investigators find that there is no constant relation between the amount of sweat and the amount of nitrogen it contains, nor is there any constant relation of the nitrogen output through the sweat to the body weight or to the temperature of the sweat-bath. An interesting fact, however, is that the relations of the amounts of the single nitrogenous substances in the sweat to its total nitrogen is relatively constant. A study of the nitrogen partition of the sweat and of the serum, simultaneously, has proved that the skin, exactly like the kidneys, has the power to excrete certain nitrogenous substances in higher concentration than they exist in the blood, but the choice of these substances by the sweat, and the degree of their concentration, differ considerably from the findings in the urine. Thus, the concentration of the urea in the sweat is to that of the blood as 3 or 10:1; whereas, the concentration of the urea in the blood compared with that in the urine is as 1:10. The relation of the ammonia nitrogen to the total nitrogen in the sweat is greater than that in the urine. Uric acid and diastase are always present in the sweat, and the concentration of both in that fluid is less than in the serum, and is less also than in the urine. Many substances are excreted in the urine which do not appear in the sweat; thus, while the kidney can excrete phenolsulphonephthalein, methylene blue, indigo-carmine and rosaniline, none of these bodies is excreted in the sweat. Moreover, no sugar appears in the sweat after injections of phloridzin. Urotropin, if given by the mouth, will appear in the sweat.

Pathological Chemistry in Renal Disease.—This will be discussed along with the clinical phenomena (see below).

4. Pathological Anatomical Findings in Renal Diseases

Glomerular Lesions.—The changes in the *glomeruli* in pathological processes have been studied by many eminent pathologists. These changes may involve (1) the capsular space and its lining epithelium, (2) the capillaries of the glomerulus, or (3) the intercapillary connective tissue. In nephritis, blood plasma may escape into the capsular space and coagulate, with the formation of fibrin. The fibrin may undergo fibrinolysis and disappear, or it may become organized, with formation of new connective tissue, causing adhesions of the walls of the capsular space to one another. When the glomerular capillary ruptures, hemorrhage into the capsular space may occur. Necrosis and desquamation of the capsular epithelium is a common lesion. In scarlatinal nephritis, marked proliferation and desquamation of the capsular epithelium, with formation of crescents, is a characteristic finding.

The capillaries of the glomerulus are often the seat of capillary thrombosis. These thrombi may be hyaline or fibrinous. Sometimes bacteria multiply within the capillary and occlude the lumen. In the so-called intracapillary glomerulitis, proliferation of the endothelial cells lining the capillary wall may lead to narrowing or complete occlusion of the lumen. Sometimes a glomerulus may be so completely transformed by pathological change as to lose its function almost entirely. Causes of such total change include necrosis, hyaline degeneration, amyloid infiltration and fibrosis. Partial injury to a glomerulus often follows proliferation of the intercapillary connective tissue, with local shrinking and lobulation of the glomerulus. The compensatory hypertrophy of uninjured glomeruli, alongside of chronic changes in other glomeruli, has already been referred to.

Tubular Lesions.—The various degenerations which affect the tubule in renal

disease have already been referred to above in connection with pathological physiology.

Lesions of the Interstitial Tissue.—In addition to the proliferation of the *interstitial tissue* already referred to, small areas of round-celled infiltration are often found in this tissue.

Attempts to separate sharply *diseases of the parenchyma* of the kidney from *diseases of the interstitial tissue* have always broken down, for every inflammation of the kidney is a *diffuse* process involving both parenchyma and interstitial tissue; but, while this is true, we are acquainted with a group of cases in which the parenchyma is predominantly involved, and with another group of cases in which the interstitial tissue is predominantly involved. The terms "chronic parenchymatous nephritis" and "chronic interstitial nephritis" may, therefore, with the limitation above mentioned in mind, be legitimately used.

Contracted Kidneys.—As regards the *contracted kidneys,* we have learned to distinguish between (1) the *primary* or *genuine contracted kidney,* which is really an atrophy most often due to arteriolar disease in the sense of Jores—the arteriolar nephropathy (see below), and (2) the *secondary contracted kidney,* which is a genuine chronic nephritis, seen sometimes in the end-stages of a chronic parenchymatous nephritis. The clinical symptoms and the pathological appearances may be very similar in the two forms, but if the history of the process be considered, the reasons for keeping these two varieties of contracted kidneys separate will be easily understood.

Clinical Diagnoses and Autopsy Findings.—Clinicians have often attempted to prophesy during life regarding the kind of kidney that will be found post mortem. While such attempts are laudable, and, to a certain extent, justifiable, neither the clinician nor the pathologist should expect such a prophecy always to be correct, any more than we can expect a pathologist, merely from seeing a kidney at autopsy, to tell us accurately just what clinical symptoms or what disturbances of renal function were demonstrable during life. One task is just as impossible as the other. Our knowledge is increasing, and it may be that the time will arrive when antecedent prophecy of the pathological histology of the kidney may be made by clinicians, and retrocedent diagnosis of clinical symptoms and disturbances of renal function can be made by the pathologist from his examination of the kidney. That time has, however, not yet come. It is, after all, not the business of the clinician to attempt the impossible; he will do well enough if he sees to it that he does not overlook important symptoms and that he discovers the deviations from normal function which can be made out by means of the methods now at his disposal.

View Point of Pathological Physiology.—The study of the pathological physiology of renal disorders has done much to dispel the pessimism which a too one-sided attention to pathological anatomical findings engendered. Just as in the study of heart disease, we have come to be less discouraged than formerly because valvular lesions are "incurable," now that we know our ability long to maintain in many patients the strength of the myocardium despite these valvular lesions, so in the study of renal diseases, clinicians need not despair because a renal lesion is in itself irreparable, since they have discovered that renal compensation can often be maintained for a long time by appropriate methods, despite the destruction of large amounts of kidney tissue.

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B. The Anamnesis in Diseases of the Uropoietic System

1. Possible Etiological Factors

In the anamnesis, besides attention to the *age, sex* and the *mode of onset* of the disease, certain etiological factors should be kept in mind, including (1) *previous infectious diseases* (tonsillitis, scarlet fever, typhoid fever, tuberculosis, sepsis, gonorrhea, etc.); (2) *acute and chronic intoxications* (phosphorus poisoning, sublimate poisoning, lead poisoning, coprostasis); (3) *pregnancy;* (4) *certain general diseases* (gout, diabetes, atherosclerosis).

When symptoms that suggest a disease of the uropoietic system are present we must try to determine whether the affection involves a *single organ* alone (urethra, bladder, ureter, kidney), or whether *two or more* of these organs are simultaneously diseased.

2. Subjective Symptoms

Among the *subjective symptoms* complained of in diseases of this system, aside from the subjective symptoms of uremia, which will be separately discussed, are (1) *pain,* (2) changes in the appearance of the *urine,* or in its quantity, and (3) *disturbances of micturition.*

(*a*) *Pain*

The place where the pain is felt, its character and duration, are helpful in diagnosis. If it have its origin in the *urethra,* micturition will be painful; if it arise in the *bladder,* there may be continuous pain above the symphysis pubis, or more often there is painful, imperative need of micturition and frequent emptying of the bladder known as pollakiuria (acute cystitis, gonorrheal ulcers, tuberculosis of the bladder).

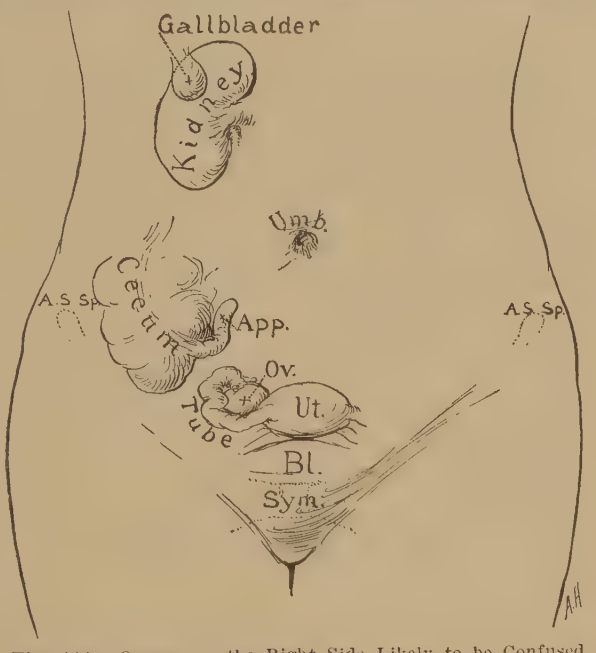

Fig. 444.—Organs on the Right Side Likely to be Confused With One Another. Rectal Examination Will Distinguish the Ovary and Tubes; Palpation in the Right Iliac Fossa Usually Discloses a Diseased Appendix: the Right Kidney May Be Examined by Injecting Its Pelvis Through the Ureter. (After H. A. Kelly.)

If the pain arise in the *kidneys,* themselves, it is usually referred to the lumbar region, whence it radiates downward along the course of the ureter to the bladder. Paroxysmal pains of this sort may be due to renal or ureteral calculus, to Dietl's crisis, or to hydronephrosis. This pain is sometimes closely simulated in chronic prostatitis (*q. v.*). In the diffuse diseases of the kidneys (acute and chronic), there may be a dull *pain in the back,* but, very often, no pain whatever is felt.

(*b*) *Changes in the Appearance and Quantity of the Urine*

Striking *changes in the urine* may be noticed and reported by patients (color, odor, sediment, etc.), but such observations are notoriously misleading, though they may emphasize the need of an objective study of the

urine and of the uropoietic organs. The patient's report regarding the *quantity* of the urine may be more important. The amount may be greatly increased (*polyuria*) or greatly diminished (*oliguria*) or urinary secretion may be completely suppressed (*anuria*). The latter must not be confused with mere *retention* of urine (see below).

(*c*) *Disturbances of Micturition*

These may depend upon local disease of the urinary passages, or they may have a nervous origin. Increased desire to urinate with frequent micturition and passage of small quantities at a time is known as *pollakiuria.* This is very common in acute cystitis, especially in inflammation of the neck of the bladder; it is sometimes the first sign of renal tuberculosis.

When micturition is difficult (*dysuria*), the condition may depend upon paralysis of the detrusor, or local obstruction in the urethra (prostatic hypertrophy; urethral stricture). In such cases, the bladder may be emptied only at abnormally long intervals, or, when the bladder becomes distended, there may be frequent but insufficient attempts at emptying (*ischuria paradoxa*), not actual retention of urine (*ischuria*).

Voluntary emptying of the bladder may become impossible; this may be due to organic obstruction in the urethra, to paralysis of the detrusor, or to abnormal mental states (hysteria; dementia praecox). *Alterations in the stream* (small volume, division of the stream, a spiral stream) may be noticed by the patient in stricture of the urethra, or when the musculature of the bladder is enfeebled.

(*d*) *Symptoms Suggestive of Uremic Poisoning*

The patient with renal disease may know nothing of his malady and may consult a physician for the first time with a complaint of some symptom which, on investigation, turns out to be a symptom due to *uremic intoxication.* As the symptoms of uremia will be discussed in detail below, they need not be gone into here. Among symptoms which should put a physician on his guard may be mentioned *headache, dizziness, muscular twitchings, temporary paralyses, anorexia, nausea, vomiting, diarrhea, dyspnea, asthma* and *disturbances of vision.*

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[NOTE.—For other references, see under Uremia (Part X) and under Urine (Part IX).]

C. The More Salient Clinical Phenomena of Renal Disease

Clinically, aside from direct tests for the functional capacity of the kidney we have to judge of *renal sufficiency* and of *renal insufficiency* (1) by the condition of the urine, (2) by the state of the blood pressure, (3) by the presence or absence of edema, and (4) by the presence or absence of the phenomena usually designated under the term uremia.

The methods of testing (5) the functional capacity, or the competency, of the kidneys will be described a little further on.

1. Abnormalities of the Urine in Renal Disease

The urine in health and disease has been fully discussed in Part IX. Certain special conditions, however, especially important for the study of renal diseases may here be referred to.

(a) *Renal Albuminuria*

Albuminuría, as we have seen in Part IX, may be due to disease of the kidney itself, or to infrarenal causes. In renal albuminuria, the process may be *transitory,* as in orthostatic albuminuria or in the toxic nephropathy of infections and intoxications, or it may be *more permanent,* as in acute nephritis, the acute toxic nephropathies, and in the chronic renal diseases (chronic nephritis; contracted kidneys). It is generally believed that in renal albuminuria the source of the protein is the glomeruli, but it cannot be definitely asserted that no protein is of tubular origin. It is quite possible that the tubules excrete it also.

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(*b*) *Cylindruria*

We have already referred to the origin of *casts in the urine* or *cylindruria,* in more than one place. Ordinary *hyaline casts* are believed to have their origin from three sources: (1) from the renal epithelium itself, (2) from the coagulation of transuded plasma, and (3) as an excretion of living tubular epithelium. *Epithelial casts* may arise from the desquamation of the original lining of the renal tubules or from the shedding of newly generated renal epithelium. *Blood casts* are formed within the tubules from blood arising from a ruptured capillary, nearly always one of the glomerular capillaries.

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[Note.—For other references, see Part IX.]

(*c*) *Hematuria, Pyuria and Bacteriuria*

Blood, pus, or bacteria may occur in the urine as the result of renal disease, but very often they have an infrarenal origin, and each case must be studied for itself to determine the source.

A true *renal hematuria* is of considerable diagnostic importance; it points definitely to diseased glomeruli. The glomerular disease may be either a diffuse glomerulitis following the effect of soluble toxins circulating in the blood, or it may be the result of a focal embolic injury of single glomeruli, or of single capillary loops in glomeruli (e. g., bacterial emboli in septic processes associated with acute tonsillitis, in endocarditis lenta, and in other infections associated with bacteriemia).

A *pyuria* is much more often due to inflammation of the urinary passages than to a purulent inflammation of the kidney itself, though in surgical kidney and in tuberculosis of the kidney, pyuria of renal origin is met with.

A *bacteriuria* may have its origin in bacteria which pass through the injured renal filter, as in typhoid fever, or it may be the result of infection from below (through the urethra, or, sometimes, by direct passage from the rectum into the bladder).

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Coli infection of the urine. Guy's Hosp. Gaz., London, ***1913,*** *xxvii, 29–33.*

(*d*) *Nocturia or Nycturia*

Frequent urination during the night is very common in renal disease, and is often the first sign noticed by the patient. When this symptom is complained of, tests of functional capacity of the kidneys should, when practicable, be undertaken.

(*e*) *Oliguria and Polyuria*

If the quantity of urine be either markedly diminished (oliguria) or markedly increased (polyuria), our suspicion should always be excited, for these symptoms often point to renal disease.

An *oliguria* associated with albuminuria and cylindruria, especially if hematuria be present, points to organic renal disease, especially to glomerulonephritis. In chronic passive congestion of the kidney (stasis kidney), we see also oliguria with albumin and casts in the urine, though in this case the signs clear up when the circulation is restored and the stasis in the kidney is overcome.

A *polyuria,* when persistent, and when associated with a urine of low specific gravity, points most often either to contracted kidney or to diabetes insipidus. It should not be forgotten that polyuria may also occur in amyloid disease of the kidney and in pyelitis. If the polyuria be asso-

ciated with a high specific gravity of the urine, one should think at once of diabetes mellitus, since this association is rare in renal disease. Polyuria is more fully discussed in Part IX and also in Part XIII (Water Metabolism).

(*f*) *Hyposthenuria*

In a great many cases of renal disease, the collected twenty-four hours urine is found to have a low specific gravity, no matter what the quantity of urine passed. It would appear that, in many of these conditions, the kidney is unable to secrete a urine of greater concentration. Such a state is known as *hyposthenuria* (von Koranyi), and it is associated with an abnormally slight depression of the freezing point, as shown by cryoscopy, and depends, as a rule, upon a diminution of the concentration of the chlorids in the urine.

According to Schlayer, a hyposthenuria can arise in either one of two ways; in the first place, it may be due to lessened excretion of solid substances, especially of NaCl; in other instances, normal amounts of solid substances are excreted, but there is an increased excretion of water. In the former instance, he believes that the hyposthenuria is due to an injury to the epithelial cells of the renal tubules (*tubular hyposthenuria*); in the latter instance, he refers the increased excretion of water to an over-sensitiveness of the renal blood vessels (*vascular hyposthenuria*).

In the **tubular hyposthenuria,** the concentration of the urine remains permanently the same, and the specific gravity is always low. The addition of NaCl to the food does not heighten the specific gravity, and the total amount of NaCl excreted in twenty-four hours cannot be increased by feeding NaCl, since the tubules cannot perform more work in this direction.

In the **vascular hyposthenuria,** the concentration of the urine also remains permanently at the same height, though the specific gravity here may be higher than in the tubular type. In the vascular type, however, NaCl added to the food is quickly eliminated, but with an increased excretion of water, so that the concentration of the urine remains the same; in other words, the renal vessels in this instance appear to be very sensitive, so that they react to every secretory stimulus by excreting larger amounts of water.

The urine corresponding to this type of vascular hyposthenuria may occur in conditions other than contracted kidney; thus, it has been met with sometimes in pyelitis, in renal tuberculosis, and in stasis kidney.

(*g*) *Hypazoturia*

In some cases of renal disease, the kidney is unable to eliminate nitrogenous substances adequately (*hypazoturic nephropathy*). This is often

met with in association with high blood pressure, with uremic symptoms and without edema. The "rest-nitrogen" of the blood is increased in amount. Sodium chlorid and water may be excreted fairly well in the urine, but the excretion of potassium iodid and of lactose may be delayed (see Functional Tests). Presumably, in such cases, the glomeruli are chiefly involved, with less change in the tubules. Studies by Rosemann and by P. von Monakow, indicate that, in such hypazoturic nephropathy, the nitrogen retained does not necessarily at first lead to marked azotemia, for apparently the nitrogen-retention occurs first in the tissues. Later on, the rest-nitrogen of the blood is increased in amount. In some instances, the rest-nitrogen may accumulate in the blood before the tissues are saturated with nitrogen; this depends especially upon extrarenal influences, as, for example, an increased protein metabolism. Great care should be exercised in drawing conclusions from brief periods of observation in such cases. To be sure of the nature of a nitrogen-retention, it is necessary to make observations over a long period, with careful control of the N-intake and the N-output (see Part XIII).

(*h*) *Hypochloruria*

In other cases of renal disease, especially in those associated with edema (so-called parenchymatous nephritis), nitrogenous substances may be very well eliminated, while sodium chlorid is retained (*dropsical, hypochloruric nephropathies*). In such cases, if NaCl be added to the food, it leads to an increase of the albuminuria, an accentuation of the oliguria, and an increase in the body weight, since when NaCl is retained water usually accumulates in the tissues. This rule does not hold absolutely. In cases in which the edema is marked, water and sodium chlorid may be retained in the form of physiological salt solution (*seroretention*). In other cases, relatively more sodium chlorid may be retained than corresponds to physiological salt solution; the edema in such cases may be slight, so that it is recognizable only by a slight increase in the body weight (*historetention*). In seroretention, extrarenal factors (for example, cardiac decompensation) may be responsible.

2. Edema and Dropsy in Renal Disease

It may be difficult to determine whether an edema is due to renal disease, to cardiac decompensation, or to some other cause (anemia; cachexia; angioneurosis).

Edema of renal origin appears to depend upon two factors: (1) upon injury to the capillaries in the *renal glomeruli*, causing obstruction to their lumina, or interfering with their capacity for contraction and dilatation, and preventing the

excretion through the kidney of common salt and water in proper amounts; and (2) a lesion of the *small blood vessels all over the body,* especially of the vessels of the skin and of the subcutaneous tissues, resulting in their increased permeability.

The edema of renal origin begins very often in the face, especially about the eyelids, and is thus in marked contrast with the edema due to stasis in chronic heart disease, in which the influence of gravity, and of distance from the heart, play a marked rôle in the distribution of the edema.

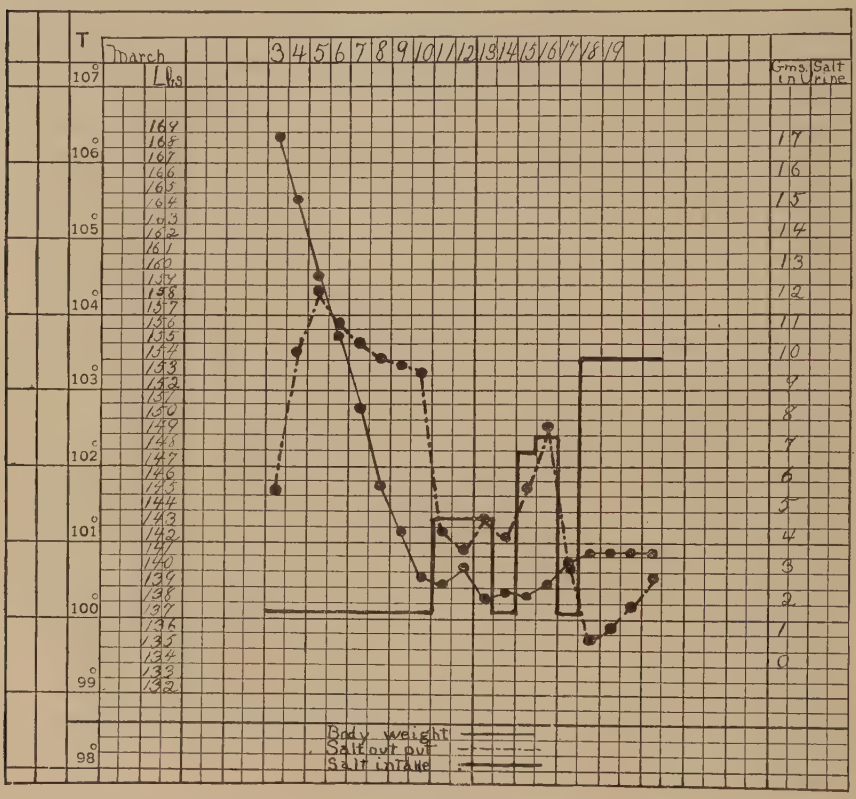

Fig. 445.—Dechloridation in a Case of Cardiorenal Edema. The Patient Lost Over 30 lbs. on a Salt-free Diet in One Week, the Edema Rapidly Disappearing. (Rosenfeld and Thornton, Med. Clinic, J. H. H.)

It cannot be too strongly emphasized that the *edema which occurs in the later stages of contracted kidney* is rarely due directly to the renal lesion itself, but depends upon a failing myocardium, and is therefore a true *stasis-edema* rather than a renal edema. A true renal edema may, of course, occur in contracted kidney if an acute nephritis be superimposed upon the chronic renal disorder.

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3. The Blood Pressure in Renal Disease

In many forms of renal disease, but by no means in all, the blood pressure is high, and this *arterial hypertension* is associated with *hypertrophy of the left ventricle;* thus, a maximal blood pressure of 160, 180, or more, associated with dislocation of the apex beat downward and lateralward, should always make one think of the possibility of contraction of the kidneys (see Part VI).

This condition is most often met with in the form of nephropathy associated with atherosclerotic disease of the fine arterioles in the sense of Jores, a disease which involves these arterioles, not only in the kidneys, but in the various organs of the body. To this form of contracted kidney, I have given the name *arteriolar nephropathy.* In such cases there may be only a trace of albumin in the urine with a few casts and a rather low specific gravity over a period of years. The patients often complain of nocturia. Not infrequently the symptoms which bring the patient to the physician are not referred by him to the kidney, but depend upon the arterial hypertension or upon beginning insufficiency of the heart muscle (headache, dizziness, fatigability, etc).

Arterial hypertension also occurs in the contracted kidney that follows the diffuse non-suppurative interstitial nephritis of Councilman and the non-suppurative exudative and proliferative types of glomerulo-nephritis that have been studied by various authors.

It would seem that arterial hypertension with hypertrophy of the heart in renal disease may occur whenever the process of urinary secretion is *largely interrupted throughout its whole cross section,* no matter what part of the kidney this involves. Thus we meet with it in (1) diffuse glomerulonephritis; (2) in sublimate poisoning with diffuse necrosis and blocking of the tubules; (3) in most contracted kidneys, especially in those due to atherosclerosis of the vasa afferentia supplying the glomeruli.

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[Note.—For other references, see Arterial Hypertension (Part VI) and Arteriolar Nephropathy (Part X).]

4. Intoxication of the Nervous System and of Other Organs in Renal Disease (Uremia)

(*a*) *Occurrence of Uremia*

When both kidneys are diseased, symptoms of intoxication of the nervous system may develop. To the group of symptoms resulting the name *uremia* has been applied. The uremic symptoms are very common just before death in a large proportion of cases of renal disease, and they may appear at times, and disappear again throughout the course of chronic renal disease, the appearance and disappearance corresponding to conditions of severer insufficiency, on the one hand, and of better compensation of the renal functions, on the other.

Under the name "uremia" a large number of symptoms have been grouped. It is very unusual to observe all of these in any one case. While the symptoms referable to the nervous system are especially common and striking, we also observe, in uremia, symptoms referable to the respiratory, the circulatory, and the digestive apparatus.

Unilateral disease of the kidney, no matter how severe, does not lead to the development of uremic symptoms as long as the other kidney functionates well. Another interesting fact is that, in *sudden complete arrest of the excretory functions of both kidneys,* as in ligation of both ureters by accident at operation with the development of complete anuria, the more characteristic uremic symptoms do not appear, though death follows in the course, usually, of ten to fourteen days.

(*b*) *Changes in the Urine and Blood in Uremia*

At the onset of uremia, there is usually a diminution in the *amount of urine* excreted, though the urinary *specific gravity* may continue to be low. The solid constituents are excreted in diminished amounts, as is shown also by an elevation of the *freezing-point* of the urine. The *total nitrogen*

of the urine and the *urea nitrogen* are usually markedly diminished just before a uremic attack, while, during the attack itself, and in convalescence afterward, there may be a distinct increase. The *acidity* of the urine is usually increased, the *ammonia-output* in the urine relatively high, and the *hydrogen-ion-content of the blood* increased, indicating a certain degree of acidosis. Corresponding to the diminished excretion of solids in the urine there is an increase of the molecular concentration of the blood (*depression of the freezing-point of the serum*). The *sodium chlorid excretion* may not be involved. The *electrical conductivity* of the urine and of the blood may remain unchanged. The urea retained in the blood may lead to increased excretion of urea through other emunctories, especially through the sweat. In some cases, crystals of urea are visible on the skin of uremic patients.

(c) *Theories Regarding the Nature of Uremia*

Toxic Theory.—The exact nature of uremia is far from clear. Formerly believed to be due to edema of the brain or to disturbances of the circulation in the brain, the consensus of opinion now is in favor of a *toxic origin* of uremia, due to retention.

Whether the toxic substances are normal end-products of metabolism, or abnormal poisons formed in disease, is not known. The old idea that urea is responsible has been given up, as has also the theory that uremia is due to ammonium carbonate formed from urea. Carbamic acid has been held by some to be responsible, owing to the findings in Eck's fistula in experimental animals. Creatinin, pigments, potassium salts, Bouchard's urotoxins, excessive molecular concentration, and failure of the internal secretion of the kidneys, have all been suggested as possible causes.

An interesting theory has been advanced by Rose Bradford. In experiments on dogs, he found that the removal of one kidney and of a part of the other was followed by an increased output of urea and of water, which he thought might be due to the loss of a normal control exerted upon the metabolic processes by the kidneys. When this control is removed, metabolism, he suggested, may run riot, so that the blood becomes over-loaded with waste-products.

Nelis Foster has isolated from the blood in uremic cases a crystalline substance, very toxic in character, which he thinks may be the cause of uremia, but as yet the definite proof of this has not been brought.

Nephrolysin Theory.—Cytolysins, known as nephrolysins, have been suggested by Ascoli and others as a cause of uremia. According to this theory, these nephrolysins not only injure the kidney tissues to which they are specifically antagonistic, but also exert a deleterious effect upon the nerve centers. But uremia may occur in renal disease in which destruction of renal tissue is not extensive (Friedrich Müller), and, moreover, uremia is often absent in cases in which there is extensive destruction of renal tissue.

In a word, *we are at present entirely ignorant of the actual cause of uremic phenomena*, though we can be sure that whatever it is, it exerts its noxious influence mainly upon the nerve centers.

(*d*) *Symptoms of Uremia*

Nervous Symptoms.—The nervous symptoms of uremia include, *convulsions,* usually of epileptiform type, and preceded, as a rule, by headache, vomiting, and dimness of vision. There may or may not be an aura. An initial tonic stage occurs, followed by clonic spasms and biting of the tongue. The fit is accompanied by tachycardia and slight elevation of temperature. The pupils are usually dilated, rarely contracted. After the fit, the patient may remain in coma for a time, or there may be simply a period of somnolence. Repeated convulsions are common. Patients often die during a fit. If they recover, temporary blindness is a common sequel.

In uremia, *temporary paralyses* are also common. Uremic hemiplegia and uremic aphasia are well known; they are probably due to temporary edema of the brain, for at autopsy no gross lesion is demonstrable except in the cases in which actual vascular lesions complicate a uremic state.

Uremic *dimness of vision* and uremic *amaurosis* are important symptoms. These may occur entirely independently of albuminuric retinitis and of choked disk. Scotomata may persist for some time after the general vision clears up. *Tinnitus aurium* and *dizziness* are common symptoms in the domain of the N. acousticus.

Aside from the coma which follows a uremic convulsion, patients suffering from uremia sometimes develop *coma* gradually after a period of drowsiness and mental torpor. Hyperkinetic phenomena (*twitchings; local spasms*) may accompany the coma. The breathing is stertorous and is often of the Cheyne-Stokes type. Instead of complete unconsciousness, there may be *delirium,* variable in degree. Sometimes outspoken *maniacal seizures* are met with, or, in the more chronic cases, *pathological ideas* (melancholic, religious, erotic, persecutory) may develop.

One of the most constant symptoms in uremia, and often the first to be complained of, is *headache.* This sometimes is very severe; indeed morphin may be required for its relief.

Digestive Symptoms.—In the digestive system, *anorexia, nausea, vomiting,* and *hiccough* are common symptoms. Sometimes there is outspoken *diarrhea,* usually attributed to an attempt of the body vicariously to eliminate the uremic poison. Whether or not the *stomatitis* and the *ulceration of the intestine,* so often found at autopsy in patients dying of uremia, are due to the uremic intoxication, or to complicating infections, is not known.

Circulatory Symptoms.—In the circulatory system, *arterial hypertension* may or may not be present. *Myocardial insufficiency* is often demonstrable, and, indeed, in some cases a uremic attack may be due to the increased insufficiency of the kidney resulting from venous stasis.

Respiratory Symptoms.—In the respiratory system, continuous *dysp-*

nea, or paroxysmal dyspnea (*uremic asthma*) are common accompaniments. Cheyne-Stokes breathing has already been referred to.

Complicating Serositides.—It has long been known that inflammations of the serous membranes (*pericarditis, pleuritis,* more rarely *peritonitis*) are frequently met with in uremic states. For a time it was thought that these were due directly to uremic intoxications. It is believed at present, however, that we have to deal in such instances with terminal infections of low grade, usually streptococcal infections.

Cutaneous Symptoms.—Of the other symptoms of uremia *pruritus,* erythematous and papular *eruptions* on the skin, and slight *fever,* may be mentioned.

(*e*) *Symptoms in Obstructive Anuria*

It has already been pointed out that complete and sudden suspension of the excretory functions of both kidneys, resulting in anuria, is rarely followed by symptoms like those which occur in chronic uremia. Such complete anuria may follow ligation of the ureters at operation, thrombosis of both renal arteries, or simultaneous obstruction of both ureters by calculi or by neoplasm. The patients die in from nine to fourteen days, as a rule, though cases have been reported where death did not occur until three weeks after obstructive suppression.

At first there may be no symptoms whatever to suggest the impending danger, but after a few days the patients grow weak and become sleepless, and toward the end of the period complain of dryness of the mouth and drowsiness. Muscular twitchings set in, but convulsions do not occur. The pupils are usually contracted. The mind may remain clear until the end, though some patients become delirious before the end. The temperature is usually subnormal. Strange to say, headache, vomiting, and the ammoniacal odor to the breath, so characteristic of uremia, do not appear in these cases of obstructive suppression.

(*f*) *Classifications of Uremia*

Various classifications of uremic attacks have been proposed. The most useful one divides the cases into those of acute, chronic, and latent uremia. Rose Bradford subdivides the acute type into (1) ordinary *acute uremia,* and (2) *fulminating uremia;* the latter develops usually without warning in patients who have long had contracted kidneys. In the dropsical form of chronic nephritis, the best examples of chronic uremic intoxication are seen. In them there may be a prolonged period of slight intoxication with nausea, vomiting, and perhaps diarrhea, before the onset of convulsions or of paralyses.

The term *latent uremia* has been used in different senses. Some apply it to the condition observed in obstructive anuria above described; others reserve it for patients in whom studies of the urine and of the blood indicate conditions which are known to be followed often by uremic attacks.

(*g*) *Diagnosis of Uremia*

The diagnosis of uremia is usually easy if the history of the patient be well known to the physician, but patients manifesting convulsions, paralyses, or coma, when first seen, may be very puzzling, and patients manifesting some one particular symptom (persistent vomiting, hiccough, Cheyne-Stokes breathing), in the absence of others, may not be recognized as uremic at first, though the further course of the disease may make the condition clear.

A careful routine examination, however, including a study of the urine, of the blood pressure, of the eye-grounds, and of the nervous functions, will rarely leave us in doubt. In the chronic cases and in the latent cases, tests of renal function are very helpful (*q. v.*).

(*h*) *The Outlook in Uremia*

The outlook in uremia is always doubtful. The patient may recover from an acute attack, and if the renal disease be an acute nephritis and end in recovery, there may be no recurrence, but when a uremic attack has occurred in the course of a chronic renal disease, even though the patient recover from the attack in which he is first seen, this will, sooner or later, be followed by others, and death will occur in one of the attacks, or by one of the other modes of termination met with in the chronic nephropathies. It is surprising, however, to see the improvement which sometimes follows catharsis, diaphoresis, venesection, or removal of cerebrospinal fluid in acute attacks of uremia. Not infrequently, however, we do most for these patients by treating the myocardial insufficiency that so frequently accompanies the attack, and which perhaps has precipitated the renal decompensation.

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D. Examination of the Kidneys by Physical Methods

1. Introduction

The kidneys lie on the two sides of the spine, extending from the level of the 12th thoracic to that of the 1st to the 3d lumbar vertebrae, reaching below to a level a few fingers' breadth above the iliac crest. The 12th rib passes across each kidney at about its middle.

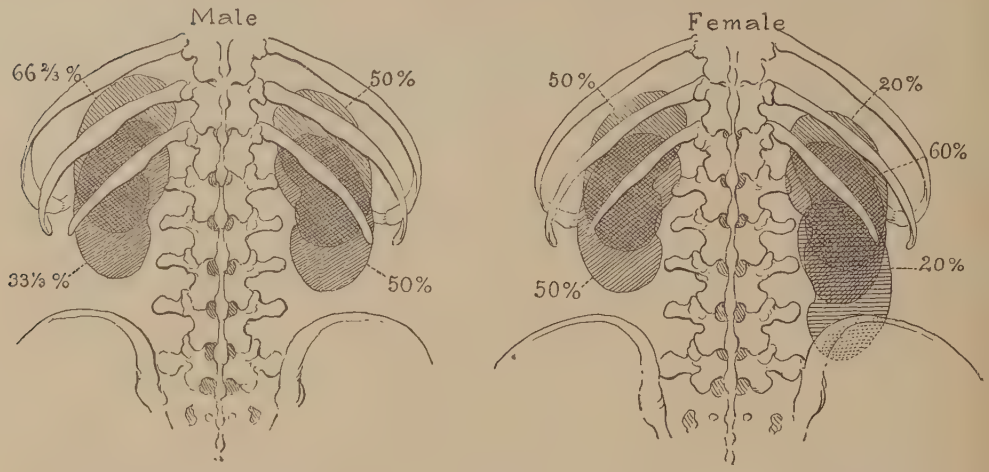

Fig. 446.—Diagrams Showing Positions of Kidney, Male and Female. The Percentages Indicate Frequency of Occurrence. Note the Low Position of Right Kidney in the Female. (After H. A. Kelly and C. F. Burnam.)

The position of the *right kidney* is a little lower than that of the left. The right kidney is in contact above with the liver; the left lies adjacent to the spleen. At the concave margin of the kidney are the renal vessels as well as the renal pelvis and the renal calices (major and minor). The structure and functions of the kidney have already been described.

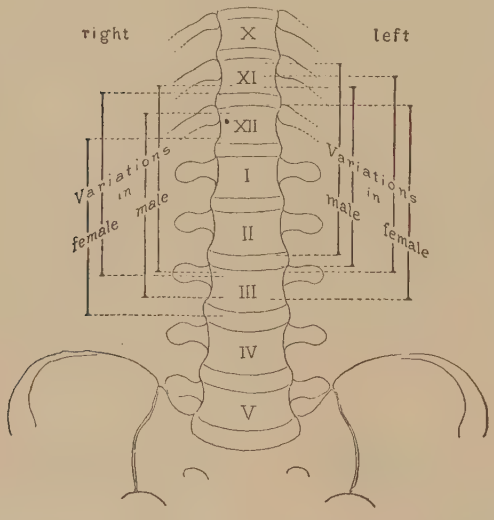

Fig. 447.—Variations in Position of Kidneys. Inside Lines, Male; Outside Lines, Female. (After H. A. Kelly and C. F. Burnam.)

In examining the kidney we depend chiefly upon (1) palpation, (2) the study of the urine from one or both kidneys, including tests of functional capacity, and (3) x-ray examination, to a slight extent; (4) inspection and (5) percussion may be of help. We shall discuss these in the customary order.

2. Inspection in Renal Diagnosis

In perirenal abscess there may be *bulging*, and, sometimes *redness* and *edema*, in the small of the back on one side. Occasionally, in large tumors or cysts of the kidney, there may also be unilateral bulging.

To inspect the lumbar region, we place the patient on a stool in a good light, and attend closely to the appearances, viewing the parts from behind

and from the side. If a very large tumor of the kidney be present, it may present in front and be visible in the flank.

3. Palpation of the Kidneys

It is well to bear in mind that if a line be supposed to be dropped, perpendicular from the mid-clavicular line, at a point two fingers' breadth below the costal arch, into the depth of the abdomen, it will certainly reach the normal kidney, for this organ extends, normally, for a distance of 5 to 6 cm. below the costal margin in the mid-clavicular line.

(*a*) *Bimanual Palpation of the Kidney*

i. The Ordinary Method

Technic.—On attempting to palpate the kidney, we make use of *bimanual palpation*, sometimes holding the liver upward by means of the thumb

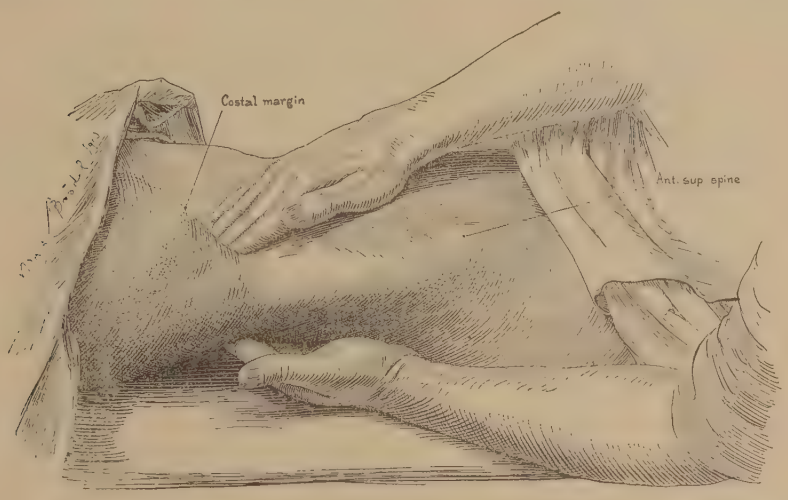

Fig. 448.—Bimanual Palpation of Right Kidney; Patient in Dorsal Posture, Left Hand Pressing Just Below the Costal Margin; Right Hand As Shown. With a Deep Inspiration, the Upper Hand Is Allowed to Follow the Abdomen Upwards and Then Presses Down Sharply With Expiration, Thus Catching the Kidney. (After H. A. Kelly and C. F. Burnam.)

of one hand. Thus, on palpating the right kidney, the right hand is placed flat upon the abdominal wall in front, and, during expiration, presses into the depth. The fingers of the palpating hand are directed upward, the tip of the middle finger reaching a point two fingers' breadth below the costal margin on the clavicular line. The fingers of the left hand press the kidney forward from behind, while the thumb of this hand holds the liver up.

In addition to the dorsal recumbent position, the lateral, the ventral, the sitting, and, especially, the upright, posture should be employed.

ii. Nephroleptic Palpation

Technic.—The *nephroleptic palpation* of Glenard is often serviceable. The patient lies on his back, and the examiner sits upon the margin of the bed at his right. The examiner's left hand grasps the flank just beneath the costal arch, the thumb in front, the other four fingers behind, and presses firmly while the right hand, with its ulnar margin upward, palpates the anterior wall of the abdomen just lateral from the umbilicus. When the kidney is palpable, a firm body can be felt as it descends on deep inspiration, slipping between the fingers.

Capture of the Kidney.—It is sometimes possible to "capture" the kidney at the end of deep inspiration, its return upward being prevented by the thumb

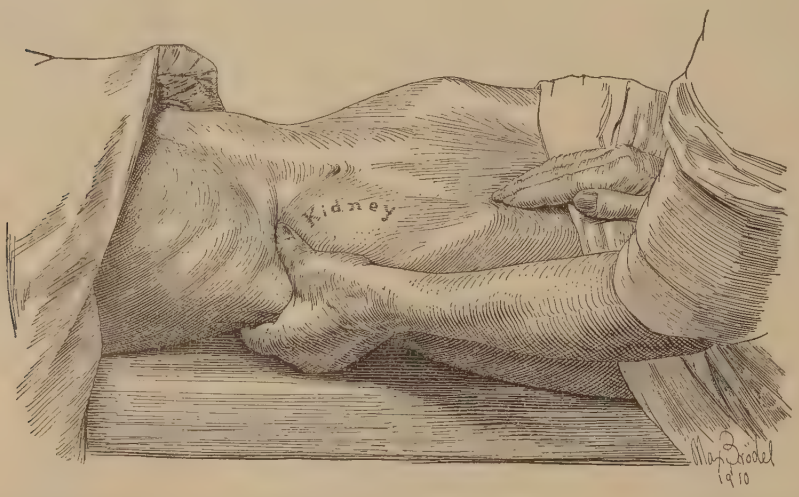

Fig. 449.—Catching and Holding the Displaced Movable Kidney So As to Prevent Its Ascending During Inspiration. This Is a Very Convenient Maneuver. (After H. A. Kelly and C. F. Burnam.)

and middle finger of the left hand, while the right hand prevents its deviation toward the middle line. In this event, its shape, volume, consistence and mobility can be judged of by means of the left thumb. When the kidney through relaxation of the pressure of the left hand is allowed to "escape," the data mentioned may be confirmed.

Another way to capture the kidney (Devoto) is to place one hand on the lumbar region and the other on the abdominal wall so that the radial margin of the index finger lies beneath the costal margin. Then, before making any pressure, the patient is told to take a deep breath; at the end of this, the posterior hand lifts the lumbar region forward while at the same time the index finger of the anterior hand is pressed into the depth beneath the costal margin. The kidney can often be felt, grasped, and held, in this way.

iii. Renal Ballottement

A third method of examining the kidney by palpation, especially to see whether or not a tumor exists, is by "renal tossing" (*ballottement* of Guyon). The kidney is given a quick thrust forward from behind, so that it can be palpated easily from the anterior abdominal wall. Thus, in bimanual palpation, the anterior hand is pressed into the depth, while, with the finger tips of the other hand, short regular thrusts forward are made in quick succession. The thrust is transmitted through the M. quadratus lumborum to the kidney lying upon it, and the fingers of the anterior hand can gain information regarding the size, shape and surface of the organ.

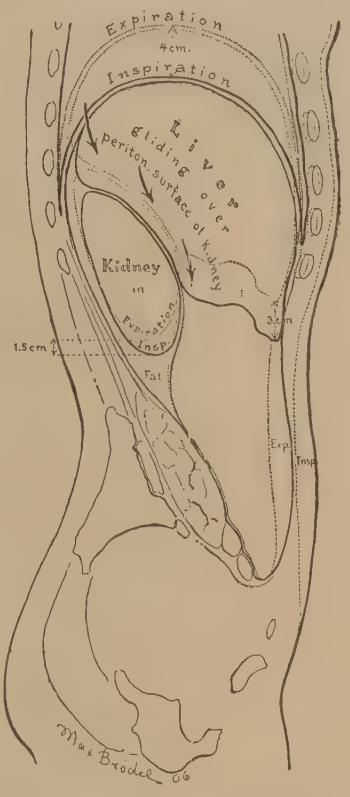

Fig. 450.—Diagrammatic Representation of Influence of Breathing on Kidney. Note How Liver Normally Glides Over It With Each Descensus of Diaphragm. A Movement Downwards of 1.5 cm. of the Kidney May Be Regarded As the Average Amount in Quiet Respiration. (After H. A. Kelly and C. F. Burnam.)

(*b*) *Findings on Palpation of the Kidneys*

i. Normal Kidneys

The *normal kidney* is not always palpable. The palpability of its lower extremity depends upon the condition of the abdominal wall and of the intestine, as well as upon the skill of the examiner. If more than the lower third, or the lower half, of the kidney be palpable on deep inspiration, the condition is abnormal. When palpable, the surface of the normal kidney is felt as a smooth, feebly convex surface, with bluntly rounded margin, nowhere showing a sharp angle, thus making it easily distinguishable from the spleen or the liver.

ii. Pathological States

In *pathological states,* it is sometimes possible to palpate renal calculi, small tumor masses or cysts in the kidney.

The **dystopic kidney,** resulting from ptosis, can be recognized by its absence from its normal position, and by the fact that it can be shoved back into its normal position (palpable kidney; floating kidney; wandering kidney). It is ten times as frequent in women as in men and is

usually associated with ptosis of other organs. The left kidney is oftener congenitally dystopic than the right.

The horse-shoe kidney resulting from congenital fusion of both kidneys lies as a rule deep in the abdomen, crossing the spine as the thyroid gland crosses the trachea.

Besides dislocation of the kidney, the organ may become palpable when **enlargement of the kidney** exists, due to tumors, cysts, hydronephro-

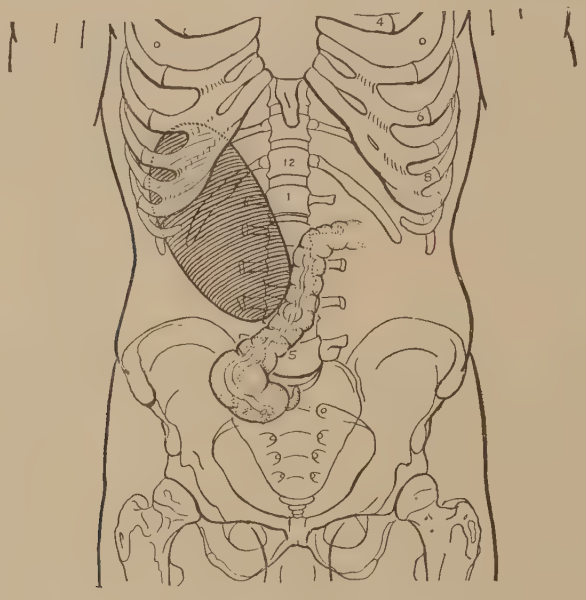

Fig. 451.—Diagram Illustrating Position of a Tumor of the Kidney on the Right Side.

sis, abscess or tuberculosis. If the kidney be *tender,* we think of renal tuberculosis, pyelonephritis or renal abscess.

A kidney may be definitely *enlarged and yet not palpable,* especially in renal calculus and in renal tuberculosis; obesity or abdominal distention from any cause may interfere with palpation.

In deciding whether a **tumor** arises in the kidney, or in the renal pelvis on the one hand, or from an adjacent organ (liver, gall-bladder, pancreas, spleen) on the other, we pay attention to (1) its exact topographical situation, (2) its relation to the gastro-intestinal tract, (3) its mobility, (4) the results of ureteral catheterization and functional renal diagnosis, (5) pain from compression of the 12th thoracic nerve and branches of the lumbar plexus, and (6) röntgenological examination.

Thus, renal tumors lie rather *lower and further to the side* than most other tumors, later growing forward toward the anterior abdominal wall so as to fill up the hypochondrium and perhaps displace the liver and diaphragm. Again,

renal tumors lie *behind the colon* when this is distended with air by a rectal tube (contrast with splenic tumors).

4. Percussion in Renal Diagnosis

This is of very little value in renal diagnosis except to demonstrate the presence of air-containing colon in front of a tumor or other enlargement of the kidney.

In the back, it is sometimes possible by percussion to determine the position of the lower poles of the kidneys and their lateral margins. One percusses upward from the iliac crest. On percussing along the spine, the note is feebler in the domain of renal, hepatic and splenic dullness, while lower down, over the lumbar spine and the sacrum the note becomes louder and more tympanitic.

It is useless to try to demonstrate contraction of the kidneys by percussion.

Fig. 452.—Large Stone in Left Kidney, Filling the Renal Pelvis and the Upper and Lower Calyces. (By courtesy of Dr. Baetjer and Dr. Waters, X-ray Dept., J. H. H.)

5. X-Ray Examinations of the Kidney and Renal Pelvis

Röntgenology is most helpful (1) in the diagnosis of renal calculus (*nephrolithiasis*), and (2) in the determination of *dilatation* or *contraction of the renal pelves,* after injection of collargol, or, better, of thorium.

(*a*) *Röntgenograms of Renal Calculi*

The gastro-intestinal tract should be thoroughly emptied (partial starvation for twenty-four hours; purge; enema). Two röntgenograms are desirable, one

Fig. 453.—Röntgenographic Diagnosis of the Urinary Apparatus. Bilateral Injection of Both Ureters and Pelves in a Woman, with 5 per cent collargol. The Entire Ureters and Pelves Are Seen and Are Normal. The Shadows of Both Kidneys Are Remarkably Clear. (After E. Legneu, E. Papin, and G. Maingot, "Exploration Radiographique de l' Appareil Urinaire," Published by Société d'éd. sc. & med., Paris.)

plate for orientation, and, if a suspicious area appear in this plate, a second plate of sharper focus, with the aid of a diaphragm over this suspicious area.

The patient lies on his back with the legs drawn up, so as to flatten the lumbar region, the plate behind him, extending from the 10th rib downward. The body is protected in front by lead plates, so that only the region between the 11th rib and the level of the iliac crests is exposed; the anti-cathode is placed 50 cm. from the plate; a soft tube with long exposure is used (see Part II).

Three different *sites* on each side for the application of the tube-diaphragm are advised by Albers-Schoenberg. In making the exposures, it is best to use a tube

with a hardness of about 7–8 Wehnelt units. In obese patients, it is a good plan to expose two plates simultaneously, their film sides in apposition with one another (double-plate method of A. Köhler). Each plate is developed separately, and after drying, the two plates are again placed in exact apposition.

On examining the plates in the light-box, one looks for (1) the 11th and 12th ribs, (2) the transverse processes of the vertebrae, (3) the iliac bones, (4) the M. psoas, extending downward from the 12th vertebra. The outline of the kidney may be visible. One looks especially for darker areas which could be calculi. If any are found, the second plate is

Fig. 454.—Pyelography. Kink in Ureter—in a Case of Orthostatic Albuminuria. Silver-iodid Injection. (X-ray Dept., J. H. H.)

exposed with the use of a tubular diaphragm (Albers-Schoenberg) which permits of marked compression of the abdomen, or a Gurt compressor is used.

Most renal calculi throw a good shadow. Calculi composed of uric acid are an exception to the rule and may be difficult to detect in röntgenograms; some röntgenologists assert that uric acid calculi cannot be so detected at all.

(*b*) *Röntgenograms of Renal Pelves*

Before exposing the plate, a warm 5–10 per cent solution of collargol may be injected into the pelvis of the kidney through a ureteral catheter. The amount which can be borne without severe pain varies. A few cubic centimeters will usually suffice for the röntgenogram, and one should never introduce more than 20 ccm. The tension of the fluid must be maintained with the piston of the syringe until after

the exposure. Patients bear the procedure better if a subcutaneous injection of morphin be first given. After the exposure, the pelvis of the kidney is carefully washed out with a warm solution of boric acid (2 per cent). When successful, the exact shape of the renal pelvis and of some of its calices and of the ureter are visible.

Fig. 455.—Normal Renal Pelvis. Injection by Gravity, Fifteen per cent Neutral Thorium Solution. Pelvis and Calyces Normal in Outline. (Courtesy of Dr. J. E. Burns.)

Recently, Burns, in Young's clinic, has been using thorium instead of collargol, owing to the danger attending the use of the latter substance. I am indebted to him for several of the röntgenograms used in the illustration of the present volume.

The danger on the right side of confusing a gall-stone with a renal stone or a ureteral stone, and *vice versa,* should always be kept in mind.

When a stone is looked for in a ureter, much care should be taken not to confuse a *phlebolith* with a ureteral calculus.

Fig. 456.—Double Pyelogram, Showing Normal Renal Pelvis on Either Side. The One on the Left Bifid in Type, also Slight Kink in the Lower End of the Ureter. Both Injections by Gravity with Fifteen per cent Neutral Thorium Solution. (Courtesy of Dr. J. E. Burns.)

The ureters are well revealed in a thorium röntgenogram; or their course can be well shown by making a röntgenogram after opaque ureteral catheters have been introduced into the ureters.

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E. Examinations of the Excretory Capacity of the Kidneys; Functional Renal Diagnosis

1. Introduction

The examination of the urine as a whole has been discussed in Part IX. In addition to what has been said there concerning the study of renal function, it seems desirable to summarize here the attempts which have been made in recent years to elaborate special methods of testing, clinically, the functional capacity of the kidneys, in other words, the ability of these organs, under controlled conditions, to purify the blood by excreting (1) water, (2) the normal urinary solid constituents, and (3) substances foreign to the body introduced especially for testing purposes. In these studies special attention is paid to: (a) the time required for the appearance of the excretion of the substance under test, (b) the length of time taken after excretion of the substance begins until all that is to be excreted has passed out, (c) the quantity of the introduced substance which can be recovered from the urine during the period of the test, (d) the concentration-relations of the substance in the urine and (e) the relations between the amount of the substance in the blood and the amount excreted in the urine at the time of the test.

As this field is, at the time of writing, being most industriously tilled, it is quite probable that there will soon be much to add to what is now put down. As the main principles have, however, already been applied, it would seem probable that the results of further work may be easily correlated with the summary here given.

We shall discuss these methods of functional renal diagnosis under the following headings:

I. METHODS WHICH DETERMINE THE WATER-EXCRETION, THE EXCRETION OF TOTAL SOLIDS AND OF ELECTROLYTES (PHYSICO-CHEMIC METHODS)

(a) Determination of Quantity of Urine and Specific Gravity.
(b) Determination of the Osmotic Pressure or the Concentration in Total Mole-ions by Cryoscopy of the Urine.
(c) Determination of the Concentration of the Urine in Total Electrolytes by Measuring the Electrical Conductivity.
(d) The "Water-Experiment" and the "Polyuria Test."
(e) The Amount of Urine and Its Specific Gravity after a Renal Test Diet Hyposthenuria.

II. METHODS WHICH DETERMINE THE POWER TO EXCRETE SPECIFIC CHEMICAL SUBSTANCES (NORMAL CONSTITUENTS OF THE URINE OR FOREIGN SUBSTANCES)

(a) Quantitative Study of Excretion of Normal Constituents.
  i. Nitrogenous Substances.
    1. Total Non-protein Nitrogen.
    2. Urea.
    3. Uric Acid.
    4. Creatinin.
  ii. Non-nitrogenous Substances.
    1. Sodium Chlorid and Water.
    2. Diastase.

(b) Excretion of Substances Foreign to the body after Ingestion or after Injection into the Blood, the Muscles, or the Subcutaneous Tissues.
  i. Phenolsulphonephthalein (Rowntree-Geraghty).
  ii. Potassium Iodid (Schlayer).
  iii. Lactose (Schlayer).
  iv. Methylene Blue, Indigo-carmine, or Rosaniline.
  v. Diuretics (Theocin; Diuretin, etc.).

III. METHODS WHICH REQUIRE A COMPARATIVE SIMULTANEOUS STUDY OF THE URINE AND THE BLOOD

(a) Nitrogenous Substances.
  i. The Total Non-protein Nitrogen of the Blood and the Urine.
  ii. The Urea of the Blood and of the Urine.
  iii. Ambard's Ureo-secretory Constant or Coefficient.
  iv. McLean's Index of Urea Excretion.

(b) Non-nitrogenous Substances.
  i. The Sodium-chlorid Content of the Blood and of the Urine.
    1. The NaCl-secretion Threshold.
    2. The NaCl-secretion Constant.
  ii. The Total Electrolytes of the Blood and of the Urine.
    (a) The Hemorenal Index.

(c) Both Nitrogenous and Non-nitrogenous Substances.
  i. Total Nitrogen and Total Chlorids (Hefter and Siebeck).
  ii. The N and the Cl of the Blood and of the Urine, together with the Water-excretion and the Specific Gravity after a Renal Test Diet (Hedinger; Mosenthal).

IV. OTHER METHODS FOR TESTING THE FUNCTIONAL CAPACITY OF BOTH KIDNEYS

(a) Determination of the Capacity to Secrete the Toxic Substances of Normal Urine (Bouchard's Urotoxic Coefficient).
(b) Determination of the Urea-content of the Cerebrospinal Fluid.
(c) Determination of the Fatigability of the Secretory Power of the Kidney.
(d) Determinations Bearing upon the Acidity of the Blood in Renal Diseases.
  i. Measurement of the CO_2 Tension of the Blood.
  ii. Determination of the Amount of $NaHCO_3$ Necessary to Render the Urine Alkaline.

V. METHODS FOR DETERMINING THE FUNCTIONAL CAPACITY OF EACH KIDNEY SEPARATELY

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2. Methods of Determining the Excretion of Water, of Total Solids, and of Electrolytes (Physico-Chemical Methods)

These were among the earlier methods to be employed in the testing of renal function. They have to deal with the water and the urinary solids as a whole, rather than with single constituents.

(*a*) *Determination of the Quantity of Urine and the Specific Gravity*

Physicians have long known the importance of recording the water-intake and the quantity of urine excreted as a guide in judging the renal functions. The *oliguria* of many cases of acute nephritis, of chronic renal disease associated with dropsy, and of chronic passive congestion of the kidneys has been generally recognized. So, also, the *polyuria* of contracted kidney has long been matter of common knowledge. The comparison of the quantity and the specific gravity of the *night-urine* and of the *day-urine* is a useful procedure, and one resorted to by most general practitioners when chronic renal disease is suspected.

The elaboration of these methods in the study of the hyposthenurias, and in the study of renal function after a renal test diet will be taken up more fully further on.

(*b*) *Determination of the Osmotic Pressure or of the Concentration of the Urine in Total Mole-Ions, by Cryoscopy*

Cryoscopy.—On cryoscopy of the urine, the *depression of the freezing-point* ($\triangle$) can be determined by means of Beckmann's apparatus. The method has already been described (Part IX). The degree of the lowering of the freezing-point depends upon the number of mole-ions in solution in the water of the urine. It is necessary to know the total amount of urine, as well as the freezing-point lowering. The latter normally varies between 1.3 and 2.2 degrees.

Valence-Value.—The so-called *valence-value* is obtained by muliplying the lowering of the freezing-point in degrees by the amount of urine in cubic centimeters. If desired, the so-called valence-value can be ex-

pressed in moles; to do this, the valence-number is divided by 1850, since the number of moles per liter of urine $= \frac{\triangle}{1.85}$. On comparing the extent of the lowering of the freezing-point with the amount of urine excreted, we get an idea of the concentration or dilution of the urine (*oligohydruria; polyhydruria*).

Valence-values thus obtained, however, are of but little diagnostic significance unless the intake of food and fluid are exactly known. This is especially true in normal cases and in cases of mild nephropathy. In the severer nephropathies, however, it is less true, since a markedly diseased kidney is prone to excrete solids and fluid in fairly constant relations, the specific gravity becoming fixed in the sense of a *hyposthenuria* already referred to. But since tests of renal capacity should be made without prejudice, it is well to make cryoscopic examinations under strictly controlled conditions of food and fluid intake. The Hedinger renal test diet (see below) serves very well for the purpose.

Normally, the valence-values for the amount of urine passed in twenty-four hours vary between 1200 and 2400, the extreme limits of normal being 800 on the one hand, and 3200 on the other. A valence-value lower than 800 points to a serious involvement of the excretory function of the kidney. The application of cryoscopy to the "water-experiment" and the "polyuria test" will be mentioned below.

(c) *Determination of the Concentration of the Urine in Total Electrolytes by Measuring the Electrical Conductivity*

Electrical Conductivity.—The number of dissociated molecules, or ions, permits one to determine approximately what proportion of the total mole-ions found by cryoscopy consists of inorganic molecules, since most inorganic molecules in the urine undergo complete dissociation, while most organic molecules do not dissociate. The method of determining the *electrical conductivity* of the urine has been described in Part IX.

Relationship of Concentration in Electrolytes to Total Concentration.—Some observers have found a fairly *constant* relationship existing between the concentration in electrolytes (Ce) and the total concentration (C), while others state that $\frac{Ce}{C}$ *varies,* in health, between 0.47 and 0.66. According to Steyrer, $\frac{Ce}{C}$ may be abnormally low in uremia, and it is lower during decompensation of the heart (stasis kidney) than when the circulation is normal. Kraus states that $\frac{Ce}{C}$ can be used as an approximate measure of renal stasis. In parenchymatous nephritis, it is interesting that the addition of NaCl to the food causes no marked change in $\frac{Ce}{C}$.

This is in agreement with the fixed specific gravity of the urine in this form of renal disease (see Hyposthenuria).

The Chlorids and the Achlorids.—A method has been devised by von Korányi for determining the *chlorids* and the *achlorids* of the urine separately. Earlier studies had shown that the chlorids may follow a different course during excretion in the urine from the nitrogenous substances and from P_2O_5 and SO_4. In most cases, the chlorids make up by far the largest part of the dissociable inorganic molecules of the urine (ions). The quotient $\triangle$, divided by NaCl, varies normally between 1.23 and 1.69 (von Korányi). If one calculates the NaCl-equivalent of the valence-value ($= a = 30 - 50$), and subtracts from this the total NaCl-content of the urine, one obtains, besides the value for the chlorids, also that for the achlorids, expressed in the amount of NaCl (a) that corresponds to the valence-value found. The NaCl-equivalent (a) is calculated on the basis that a one per cent solution of NaCl possesses a freezing-point lowering power of 0.613°. If the amount of urine is x and the lowering of the freezing-point is $\triangle$, then $a = \frac{\triangle \cdot x}{61.3}$. One can also calculate the valence-value for the chlorids (V_1), and so inform himself regarding the reciprocal relations of the chlorids and the achlorids.

(*d*) *The Water-Experiment and the Polyuria Test*

Special methods have been devised for studying the reaction capacity of the kidney after drinking water. Here belong (1) the water-experiment of Kövesi and Róth-Schulz, (2) the water-experiment of H. Strauss, and (3) the polyuria test of Albarran.

Kövesi and Róth-Schulz allow the patient in the late forenoon or afternoon to drink 1.8 liter of Salvator water in the course of an hour; they then determine the amount of urine and its freezing-point in portions passed every half hour during the next five hours.

H. Strauss, for his water-experiment, has the patient drink 500 c.c. of water on an empty stomach in the morning; the evening before, he is permitted to take only 500 c.c. of an unsalted milk soup. The patient is instructed to empty the bladder before the beginning of the experiment, about 10 P.M., and again at 5 A.M. No food or liquid is taken for the five hours following the drinking of the water at 6 A. M. The amount of urine, the lowering of the freezing-point, and the NaCl-content are determined, and in this way the total osmotic valence for the five hours, the total NaCl-content, the relation of the chlorids to the achlorids, and the appearance or non-appearance of a depression of the freezing-point-lowering during the experiment are gotten at.

It was these physico-chemic experiments that first gave us definite clues for the recognition of the kind and degree of compensation, or decompensation, in renal disease. In well-compensated cases of nephropathy, no matter of what kind, the values lie within physiological limits, though there is a tendency to a polyhydruria with a subnormal freezing-point-lowering, which permits, however, of normal figures for the valence-value and for the value $\frac{\triangle}{NaCl}$. In renal insufficiency, however, with marked

disturbance of compensation, there is an abnormal depression of the freezing-point-lowering — the condition that von Korányi described as *hyposthenuria*—with a normal amount of urine; there is an oligohydruria, so that the valence-value does not reach the normal height. The cause of the hyposthenuria in such cases is, usually, a faulty excretion of the chlorids; hence, as a rule, the quotient $\frac{\triangle}{NaCl}$ grows larger.

On using Strauss's water-experiment, one can often make out a diminution, or an absence, of the "dilution-reaction" that ordinarily appears in the second or third hour after drinking water. Connected with the oliguria and with the appearance of subnormal valence-values, as well as with the increase of the quotient $\frac{\triangle}{NaCl}$, there is often also a delay in the change, or a total lack of the change, in the value for $\triangle$, while in well-compensated nephropathies, the influence on $\triangle$ of the water imbibed in the second or third hour after it is drunk is usually just as prompt, or almost as prompt, as in health (H. Strauss).

(e) *The Amount of Urine and the Specific Gravity after a Renal Test Diet*

The *character of a hyposthenuria* can be fairly well studied simply by recording the water-intake and the amount of urine excreted, and its specific gravity, after a renal test diet (see below). If no other examination were made, this method would naturally fall under the present heading. As, however, it is now customary to study the *blood,* as well as the *urine,* in the hyposthenurias, the description of the method and of the renal test diet will be deferred to a subsequent paragraph.

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3. Methods of Determining the Power of the Kidneys to Excrete Specific Chemical Substances (Either Normal Constituents of the Urine or Foreign Substances)

(a) *Normal Constituents*

Of the normal constituents whose quantitative excretion may be followed as a test of renal function, may be mentioned: (1) certain nitroge-

nous substances (total non-protein nitrogen, urea, uric acid, creatinin), and (2) certain non-nitrogenous substances (sodium chlorid and water, and diastase). It has been found, however, that, for the majority of these substances, there is but little use in making the test unless the blood is also examined simultaneously, or unless accurate balances (in the metabolic sense) are kept, with study of the total intake and the total output of the substances.

The methods employed when both blood and urine are studied simultaneously are described below. The methods employed in the following accurately of the different balances are described under metabolism (see Part XIII).

It would seem that a study of the quantitative excretion of *creatinin* and of *diastase* may be of some value by themselves. For the use of creatinin in this way, the articles of Neubauer, of Kraus and of Hoogenhuyze may be consulted.

i. The Use of Creatinin in Functional Renal Diagnosis

Neubauer examines the creatinin excretion in six-hourly periods on three successive days—one "preparation day," one "main day" with the addition of 1.5 g. creatinin to the diet, and an "after day." The creatinin used is that made by the Bayer Dye Works in Leverkusen, put up under the name of Ilun. The creatinin is determined by Folin's colorimetric method, which makes use of picric acid and NaOH and the Autenrieth colorimeter. The apparatus is especially calibrated by means of a pure solution of creatinin (0.1–1.2 parts per 1,000).

Normally, examined in six-hourly periods, the creatinin excretion goes on in the form of a horizontal curve. The amount excreted, if excessive meat eating be avoided, is independent of the food-intake, so that the maintenance of a rigidly monotonous diet is superfluous. If 1.5 grams of creatinin be taken in sweetened water by a normal person, about 60–90 per cent is excreted in the first period, and in the second period 8–30 per cent more, so that, in the twelve hours, 70–100 per cent of the amount swallowed is already eliminated. When the renal function is disturbed, there is a delay in the excretion, which may even extend over into the next day. Disturbance of creatinin excretion is especially marked in bilateral renal disease.

The method does not permit one to draw conclusions regarding a definite lesion, and so it cannot be used for the classification of the different nephropathies. Neubauer found delayed elimination sometimes in cases of arterial hypertension when he had no other clues pointing to disease of the kidneys. Excretion was also delayed in cases of gout, in which there were no certain signs of renal disease demonstrable. He thinks, therefore, that the early stages of a gouty kidney may perhaps be recognizable by this test. In chronic passive congestion of the kidney, disturbances of creatinin excretion were also observed. The method may be applied to the diagnosis of unilateral affections on ureteral catheterization, since differences greater than 20 per cent between the elimination on the two sides point to pathological changes.

The determination of the amount of creatinin in the *blood* may also be used as an indicator of damaged renal function. In normal serum there is, as a rule, less than 1 *mg.* of creatinin in 100 *c.c.* In uremia, the amount is considerably

increased; in one case studied by Neubauer, 20 *mg.* were present in 100 *c.c.*, along with 245 *mg.* of rest-nitrogen.

ii. Determination of Uric Acid in the Urine as a Functional Renal Test

The uric acid excretion has been followed especially by R. A. Kocher in some of the nephropathies, but the use of the method has not yet been generally applied in functional renal diagnosis. It may be valuable in the early diagnosis of the gouty nephropathy. Obviously, the patient must be placed on a purin free diet until the endogenous uric acid output is known, and then a known amount of nucleic acid given by mouth, and the excretion watched (see Metabolism of Purins, Part XIII).

The colorimetric method of Folin and Denis is the best one to use.

iii. Determination of Diastase in the Urine as a Test of Renal Function

The excretion of diastase in the urine has been followed by Geraghty, Rowntree and Cary, by Geyerlin, and especially by Pirondini. All of these observers use Wohlgemuth's method (see Part IX) for the determination of the diastase. The results seem to be in accord with those yielded by the phenolsulphonephthalein test (see below), except in cases in which there is either marked hematuria or marked polyuria. The test does not possess any special advantages and can, probably, without loss, be discarded as far as functional renal diagnosis is concerned.

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(*b*) *The Excretion of Substances Foreign to the Body after Ingestion or after Injection into the Blood, the Muscles, or the Subcutaneous Tissues, as Tests of Renal Function*

Under this heading we shall consider: (i) phenolsulphonephthalein; (ii) potassium iodid; (iii) lactose; (iv) methylene blue, indigo-carmine, and rosaniline; and (v) certain diuretics, including theocin and diuretin.

i. The Phenolsulphonephthalein Test

(*Rowntree and Geraghty*)

The phenolsulphonephthalein test, introduced by Rowntree and Geraghty, is the most important recent addition to our methods for measuring the functional efficiency of one or both of the kidneys. To insure free secretion, the patient is given from 200 to 400 c.c. of water, twenty or thirty minutes before making the test. The bladder is emptied by aseptic catheter, the exact time noted, and with an exactly calibrated syringe, 1 c.c. of the test solution (= 0.006 gram of the chemical) is injected intramuscularly, in the lumbar region. The catheter is left in the bladder until the drug begins to be be excreted, or the urine, as it drops out of the catheter, is collected in a test tube containing a drop of NaOH solution (25 per cent), until a faint pinkish tinge appears (time noted). The catheter may then be withdrawn, and the patient voids at the end of one hour, and again at the end of two hours, each voiding being

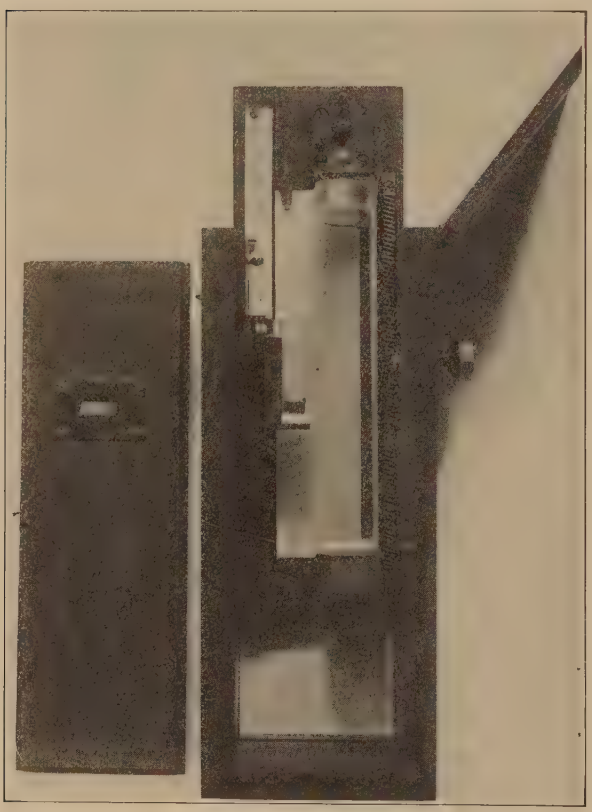

Fig. 457.—Rowntree and Geraghty's Modification of Autenrieth and Königsberger's Colorimeter. Designed Especially for Determinations of Phenolsulphonephthalein Output in Tests of Renal Function.

separately collected. The amount of phenolsulphonephthalein in each receptacle is quantitatively determined by means of a colorimeter, after taking the specific gravity, rendering the specimen strongly alkaline with NaOH, and diluting it to one liter with distilled water. If there be turbidity due to precipitated phosphates, a portion may be filtered through a dry folded filter before making the colorimetric reading. With Rowntree and Geraghty's modification of the Autenrieth-Königsberger colorimeter, the percentage can be read off at once, by noting the position of the indicator on the scale.

If the elimination be much impaired, it is better to dilute the urine to 500 ccm. rather than to 1 *l*, and to make a corresponding correction of the reading by dividing by 2.

Normal persons excrete from 50 per cent to 65 per cent (average 57.5 per cent) in the first hour. By the end of the second hour, 70-90 per cent of the amount injected should be excreted. When renal efficiency is impaired, the output may be, quantitatively, greatly decreased, and the excretion is delayed.

This method has been used for a large number of my patients (with and without nephropathies) and when the output is low I consider it a valuable indicator of renal insufficiency. When the output is high, we can feel fairly sure that, even though an extensive renal lesion is present (as in contraction of the kidneys), there is temporarily renal compensation. The mistake should not be made, however, of assuming, because the phthalein-output is normal in amount, that there is no anatomical change in the kidneys. For very extensive renal lesions may exist with a normal, or nearly normal, phthalein output. The test is of renal *function*, not of the gross renal *structure*.

In impending uremia, whether in acute nephritis, in chronic parenchymatous nephritis, or in contracted kidneys, the phthalein output is usually very low. Occasionally, a very low output may be found without signs of uremia; I have been especially impressed by the great reduction of phthalein-output in certain cases of double congenital cystic kidney not followed (at least for many months) by uremic symptoms.

In stasis-kidney, the phthalein-output is somewhat impaired, but less than in chronic nephritis with dropsy. My colleague, Dr. W. S. Thayer, has made a careful analysis of the autopsies on 50 cases in which during life the renal function had been tested with the phenolsulphonephthalein test and other functional tests.

Comparisons of the phthalein test with other functional renal tests have been made by several observers (Rowntree and Fitz, Schlayer, Herringham and Trevan, N. B. Foster, Geraghty, Rowntree and Cary, Goodman). The limitations of the test have been discussed by M. Roth. Instances of increased permeability of the kidney to phenolsulphonephthalein have been reported by W. A. Baetjer.

ii. The Potassium Iodid Test

The patient receives 0.5 gram of KI, in solution, by mouth, and the urine is tested every two hours for iodin. A little chloroform is added to the urine, then a few drops of sodium nitrite solution, and a few drops of dilute H_2SO_4. Shake well, and the free iodin will be dissolved in the chloroform. Instead of the use of chloroform, we may add the $NaNO_2$ and the H_2SO_4, and then a little starch solution, which will turn blue in the presence of free iodin.

Normally, excretion is complete in from 30 to 55 hours after the intake. In certain renal diseases, the excretion is prolonged beyond 60 hours, in which event, according to Schlayer and Takayasu, it may be assumed that excretion through the renal tubules is faulty.

iii. The Lactose Test

Twenty grams of milk sugar (lactose) dissolved in 20 c.c. of distilled water (a solution of this concentration having been previously pasteurized at 75° to 80° for four hours on each of three successive days) is injected, under aseptic precautions, into a vein at the bend of the elbow. The urine is collected at hourly, or half-hourly intervals, and tested with Nylander's solution until the reaction for sugar ceases to be positive.

Normally, the lactose is all excreted in from 4 to 5 hours. In many cases of renal disease, the excretion is not completed in 7, 9, 12 or more hours. According to Schlayer and Takayasu, such delayed lactose-excretion is a sign of disease of the renal blood vessels (glomerulonephritis; arteriolar nephropathy with contraction).

iv. Methylene Blue, Indigo-carmine and Rosaniline Tests

In making the *methylene blue test,* 5 *cgr.* of chemically pure methylene blue in sterile aqueous solution (1:20) are injected subcutaneously, after which the patient urinates every half hour for three hours, and then at longer intervals (after 24 hours at three-hourly intervals), until the green discoloration has disappeared from the urine. One determines (1) the time when the blue or green color first appears, and (2) the time when it disappears.

Normally, either methylene blue or its chromogen will appear in the urine at the end of the first half hour, will reach its maximum at the third or fourth hour, and will disappear completely after from thirty-six to forty-eight hours.

The method is no longer much used, since better tests of renal function have come into vogue. In contracted kidney, the excretion may not be completed until after four or six days.

Indigo-carmine and *rosaniline,* which played an important part at the beginning of studies of renal function, have, of late, been practically discarded as functional renal tests.

v. Diuretic Tests

The capacity of the renal epithelium to respond to specific stimulation can be determined by the administration of various diuretics. Among the most serviceable may be mentioned (1) *theocin,* (2) *diuretin,* (3) *caffein,* and (4) *urea.* The conditions of food and fluid intake should be strictly controlled before the test dose of the drug is given.

In certain cases of chronic parenchymatous nephritis, studied by P. von Monakow, it was found that there was no parallel between delayed lactose excretion and a poor diuretic effect of theocin. Erich Meyer has shown that the administration of theocin can, even when lactose-excretion is delayed, be followed by increase in the NaCl-concentration of the urine. Many believe that delayed lactose excretion points to diseased glomeruli and that theocin-diuresis points to capable renal epithelium.

It is stated that the diuretic effect of theocin may fail in polyuria and be present in oliguria; urea, on the other hand, it is asserted, always causes diuresis in the hypochloruric nephropathies, and can sometimes be used with benefit therapeutically when theocin and diuretin fail (P. von Monakow).

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4. Methods that Require a Comparative Simultaneous Study of the Urine and the Blood

Here again the tests may make use of (a) nitrogenous substances alone, (b) non-nitrogenous substances alone, or (c) both nitrogenous and non-nitrogenous substances at the same time.

(a) *Simultaneous Study of the Nitrogenous Substances of the Urine and of the Blood in Functional Renal Diagnosis*

In this study the two most important methods are (i) the determination of the total non-protein nitrogen, and (ii) the determination of the urea, or of the urea nitrogen.

i. Determination of the Total Non-protein Nitrogen of the Blood and Urine

When the total non-protein nitrogen is studied simultaneously in the blood and in the urine, important conclusions can be drawn regarding renal function. The older studies on this point are practically worthless, but recent studies, especially those in which Folin's methods have been used for the determinations, have yielded interesting results. The term rest-nitrogen is probably best avoided, since it is used by different authors in entirely different senses.

The most interesting results are obtained in the cases in which the nitrogen-output in the urine is diminished (*hypazoturic nephropathies*). We have already referred to this class of cases above, and have mentioned some of the findings that have been recorded and their bearing upon hypazoturia, azotemia, and tissue retention of nitrogen.

In making the tests, the food and fluid intake must be strictly controlled, qualitatively and quantitatively. It is probably best to make the test in association with a renal test diet (see below). In blood analyses made by Folin and Denis (1913), the total non-protein nitrogen varied in 16 *normal persons* only between 22 and 26 *mgm.* per 100 *g.* of blood. In their experiments, the blood was taken 3-6 hours after breakfast, but when *patients* were studied, whether they suffered from renal disease or not, much larger values were obtained.

McLean and Selling (1914) found that the total non-protein nitrogen of the blood varies *normally* between 23 and 36 *mgm.* per 100 *c.c.* They conclude from their studies that the concentration of total non-protein nitrogen in normal blood is not constant, but varies within wide limits, according to various factors of diet, amount of fluid ingested, etc. They point out that it is best to make the examinations correspond to short periods (1-2 hours) for the urine, the blood being collected at the middle of the period; tested in this way, the amount of urea in the blood may be safely assumed to represent the average concentration for the period, in case no food or liquid has been taken during the period.

McLean, in a later paper (1915), states that "the normal concentration

of urea in the blood varies from about 0.200 to 0.500 grams per liter, in the same or different individuals. The rate of excretion is determined by this concentration and by the rate of water output."

ii. Determination of the Urea-content of the Blood and of the Urine

In 16 *normal persons,* Folin and Denis found the urea-nitrogen to vary between 11 and 13 *mgm.* per 100 *g.* of blood, the blood being drawn in the morning, 3 to 6 hours after breakfast. Just as with the non-protein nitrogen, however, this constancy of the urea-content of the blood did not hold when they came to examine *patients.* Unfortunately, no report of the urea-content of the urine was made.

Marshall and Davis (1914), working on experimental animals with Marshall's methods for the determination of urea in the blood and in the urine, found that the rate of excretion of urea in *normal animals* is directly proportional to its concentration in the blood. They further found that the elimination of urea in urine may be retarded by *dehydration* of the organism.

Ambard, as a result of the study of normal human beings, has asserted that (1) when the concentration of urea in the urine is constant, the quantity of urea excreted in the urine varies proportionately to the square of the concentration of the urea in the blood; thus,

$$\frac{(\text{Urea in blood})^2}{\text{Rate of Excretion}} = \text{Constant, or} \frac{\text{Urea in blood}}{\sqrt{\text{Excretion per unit of time}}} = \text{Constant}$$

And (2) when the concentration of urea in the blood remains constant, the quantity excreted in the urine varies inversely as the square root of the concentration in the urine; thus,

$$\frac{\text{Rate of excretion I}}{\text{Rate of excretion II}} = \frac{\sqrt{\text{Concentration II}}}{\sqrt{\text{Concentration I}}}$$

It was from these laws that he formulated his *urea-secretory-constant* or *urea-coefficient* (see below).

Very careful studies, including simultaneous estimations of the total non-protein nitrogen and the urea-nitrogen of the blood, and of the total nitrogen and the urea-nitrogen of the urine have been made by McLean and Selling (1914).

The results and conclusions of the French school had been criticized by American writers on account of the inaccurate methods used for the determination of urea. McLean and Selling, in their work, made all their determinations by the

methods described by Folin and his collaborators. Compressed air under high pressure was used for driving off the ammonia, a precaution necessary to observe if accurate results are to be obtained, for the findings with the use of the vacuum-pump were entirely unreliable. For colorimetric readings, they made use of a new model Kennicott-Sargent colorimeter. In one series of experiments, they made use of a *24 hour period,* the total urine for that period being collected, and the blood withdrawn once during the day. The results obtained by this method were inaccurate, since the urea of the blood fluctuates from hour to hour, and the urea-content of the blood at the time of examination was not always representative of the average of the concentration during the 24 hour period. In most of their studies, therefore, they made use of a *shorter period,* usually one hour, and the blood was collected at the middle of this period. By the latter method, the amount of urine in the blood, they think, can be safely assumed to represent the average concentration for the period, in case no food or fluid has been taken during the period.

McLean and Selling find that there is a close parallelism between the concentration of urea in the blood and the amount excreted in the urine in *normal persons* under average conditions. They have confirmed for man the statement of Marshall and Davis (based upon animal experiments) that the elimination of urea may be retarded by *dehydration* of the organism. They find, further, that a concentration of urea-nitrogen as high as 22 *mgm.* per 100 *c.c.* of blood does not necessarily indicate any disturbance in elimination of urea unless associated with a relative decrease in the amount excreted (see Ambard's coefficient). The urea-nitrogen of the blood in *normal persons* (not including the tests made after the ingestion of urea) varied in their series from 10-23 *mgm.* per 100 *c.c.* of blood. They maintain that the absolute amount of urea in the blood cannot be taken as evidence of "nitrogen retention" since the concentration of urea in the blood in the cases of *frank nephritis* with other evidence of impaired elimination studied by them does not differ materially from that met with in many normal persons.

In a later paper (1915) McLean says that he has not observed a concentration of urea in the blood above 0.500 in a normal person under ordinary circumstances.

Thévenot has studied 22 patients suffering from chronic renal disease. He found that those whose blood urea was less than 0.7 *g.* per liter lived at least five or six months, while four patients with urea-values in the blood between 2 and 8 *g.* per liter, quickly died.

Widal and Javal have reported that, in their experience, urea-values in the serum between 1 and 8 *g.* per liter are an indication that death will soon follow, while when the quantity is between 0.5 and 1.0 *g.* per liter, the prognosis is doubtful. They made repeated tests in many cases that showed that the urea-value of the serum can remain unchanged for years, or that it may progressively rise. They conclude that if the blood-urea is only slightly increased, it is necessary, in order to be sure of the prognosis, to make repeated examinations of the blood serum at long intervals.

iii. Determination of Ambard's Ureo-Secretory-Constant

Ambard, after formulating the two laws mentioned above regarding urea in the urine and urea in the blood, devised what is called the *ureo-secretory-constant,* determined by a formula known as the *urea-coefficient,* obtained by making corrections (1) for the weight of the individual and (2) for the average concentration of the urea in the urine, which he takes to be 25 *g.* per liter. His formula, or urea-coefficient, is as follows:

$$K(\text{constant}) = \frac{Ur}{\sqrt{D} \times \frac{70}{P} \sqrt{\frac{C}{25}}}$$

Ur = Urea per liter of blood, in grams.
D = Urea in urine in twenty-four hours, in grams.
P = Weight of patient, in kilos.
C = Concentration, or grams of urea per liter of urine.

Ambard and other French observers assert that K is constant in *normal persons;* they maintain that it varies only between 0.06 and 0.07 under varying conditions of diet. But in *cases of nephritis,* associated with a relative increase in the concentration of urea in the blood, and a decrease in the elimination of urea in the urine, they found an enormous increase in the value of K. The French clinicians have come to lay great stress upon the value of the determination of this constant in the diagnosis and prognosis of the nephropathies.

Unfortunately, the methods used by the French investigators for the determination of urea (hypobromite method) are inaccurate as compared with the very precise methods that have been worked out in the United States by Folin, on the one hand, and by Marshall, on the other. Recently McLean and Selling have submitted the whole matter to careful control, making use, in their studies, of the exact methods of Folin. They conclude that "Ambard's coefficient, when computed from results obtained by the accurate methods of Folin and his collaborators, varies in normal persons only between comparatively narrow limits, and may be regarded as constant," and, further, that "ingestion of urea does not materially alter the value of Ambard's coefficient, provided sufficient time is allowed for absorption before examination is made." It would appear that with accurate urea-determinations, Ambard's constant in normal persons is about 0.080 (McLean).

We cannot do better, perhaps, than to illustrate the point by reproduction of a portion of the tables published by McLean and Selling:

RESULTS IN NORMAL PERSONS. LENGTH OF PERIOD, ONE TO TWO AND ONE-HALF HOURS

Subject	Weight	Date	Period	Blood (Mgm. per 100 c.c.)			Urine							Ambard's Coefficient	Remarks
							Amount c.c.		Grams in 24 hours			Grams per liter			
				Non-protein N	Urea N	Urea	Period	24 Hrs.	Total N	Urea N	Urea	Urea N	Urea		
	Kilos														
F. C. M.	77.2	IV, 29	9.15–10.15	30	17.0	36.3	40	960	....	13.7	29.3	14.6	31.2	0.065	
	77.2	V, 6	9.15–10.15	30	12.0	25.6	177	4248	16.1	14.6	31.2	3.6	8.0	0.064	
	77.2	V, 11	2.45– 3.45	28	15.0	32.1	83	2000	14.2	13.0	27.8	6.5	13.9	0.078	
	77.2	V, 18	2.45– 3.45	27	18.0	38.5	40	960	11.1	10.3	22.0	10.8	23.1	0.087	
	77.2	V, 21	11.00–12.00	27	15.0	32.1	34	816	....	9.4	20.1	11.6	24.8	0.075	
	77.2	V, 25	3.30– 5.30	44	24.0	51.3	128	1536	25.2	24.6	52.6	16.4	35.1	0.068	45 minutes after urea, 10 gm.
	77.2	V, 28	2.45– 3.45	28	19.0	40.6	101	2424	35.8	29.6	63.3	11.8	25.2	0.053	3 hours after urea, 10 gm.
	77.2	VI, 1	10.00–11.00	23	14.0	29.9	30	720	7.9	6.9	14.7	9.7	20.7	0.085	3 days protein-poor diet.
R. A. S.	70.0	V, 5	4.00– 5.00	36	15.0	32.1	155	3720	15.5	13.7	29.3	3.8	8.1	0.078	
	70.0	V, 12	3.30– 4.30	29	17.0	36.3	38	912	9.8	8.8	18.8	9.7	20.7	0.087	
	70.0	V, 25	3.45– 4.45	31	20.0	42.8	78	1872	21.6	20.1	43.0	10.8	23.1	0.065	1 hour after urea, 5 gm.

Results in Positive Nephritics. Length of Periods, One to Twenty-four Hours

Subject	Weight	Date	Blood (Mgm. per 100 cc.)		Urine				
					In 24 Hours			Per Liter Urea N	Ambard's Coefficient
			N	Urea N	Amt.	N	Urea N		
					cc.	Grams.	Grams.	Grams.	
B.....	70	V, 23	50	29	1250	10.3	9.6	7.6	0.150
A.....	70	V, 30	41	25	1500	12.7	11.9	8.0	0.116
J.....	90	V, 21	43	27	1380	13.2	12.4	9.0	0.135
E.....	52	V, 12	31	24	744	9.4	8.8	11.8	0.127
R.....	66	IV, 7	25	15	1000	6.6	5.8	5.8	0.105
B.....	70	IV, 23	36	19	860	8.9	8.0	9.4	0.103
H.....	70	VI, 2	40	26	720	9.0	7.6	10.6	0.141

These are very striking figures. It would be interesting to know just what is meant in the second table by "positive nephritics." Very soon, doubtless, we shall have studies in a whole series of different kinds of nephropathies, and from these we may be able to decide just what the meaning of a high value for Ambard's coefficient is.

iv. McLean's Index of Urea Excretion

In 1915, McLean published a paper in which he adds materially to the former contribution of McLean and Selling (see above).

When the coefficient of Ambard is used, changes in the excretion of urea are expressed by variations in the value of K, and these variations must be expressed on an arbitrary scale. Values for K, for example, increase directly with increase in Ur, other factors remaining the same. Changes in K then reflect changes in the urea of the blood, these changes occurring as the square root of changes in the rate of excretion (see above).

McLean, "in order to express the changes in rate of excretion in a manner mathematically correct and based on a scale of 100 for the sake of comparison," has used a formula adapted from the laws of Ambard, which he calls an "index of urea excretion."

An index of 100, corresponding to a value for Ambard's coefficient of 0.080, is the standard normal index, and variations can be expressed directly in terms of the normal. Thus a McLean index of 50 indicates a rate of excretion 50 per cent of normal under the conditions of concentration in the blood and urine.

McLean's index can be simply derived from Ambard's coefficient after this has been determined. Thus:

$$I = \text{Index of Urea Excretion} = \frac{\text{(Rate of excretion found)}}{\text{(Standard normal rate)}} \times 100$$

(under the same conditions of weight, and concentration in blood and urine).

If McLean's assertion that Ambard's constant $= K = 0.080$ in normal persons, then his index for the normal $= 100$. An index of 80 is, according to McLean, the lowest compatible with normality. Along with the urea excretion he calculates the theoretical concentration of sodium chlorid in the plasma (see below).

Technic.—"One-half hour after the patient drinks 150 to 200 c.c. of fluid, the bladder is emptied and the subject takes no further fluid or food until a carefully timed period, usually of seventy-two minutes, is ended. The urine excreted during this period is collected, and at the middle of the period about 10 c.c. of blood are withdrawn from an arm vein, clotting being prevented by a small amount of powdered potassium oxalate. The choice of a period of seventy-two minutes is merely for the sake of convenience, seventy-two minutes being one-twentieth of twenty-four hours. A one or two hour period may, of course, be used, all calculations in any case being made on a basis of twenty-four hours. In case an error of a few minutes is made in the time of collection of the second specimen, the calculation should be made on the basis of the time actually elapsed between the voiding of the first and second specimens. The amount of urea in the whole blood, and total chlorids, estimated as sodium chlorid, in the oxalated plasma after centrifugalization, are determined. Both urea and chlorids are determined in the urine. By substituting the values obtained in the proper formulas the relationship of the rate of excretion of these substances to their concentration in the blood is determined. In the case of urea the rate of excretion under the conditions found is directly measured in terms of the normal, by the use of the following formula:

$$\text{Index of urea excretion} = \frac{8.96 \times \text{Gm. urea per 24 hrs.} \sqrt{\text{Gm. urea per liter of urine}}}{\text{Wt. in kilos} \times (\text{Gm. urea per liter of blood})^2}$$

Calculation.—The substitution of values found by analysis in the formulas and the calculation of the formulas is in itself a considerable task if the ordinary arithmetical processes are used. Logarithms are of advantage, but they are also laborious. To simplify the process of calculation, and thereby reduce both the labor and the chances of error, a slide-rule has been adapted to the formulas. By the use of this device it is not even necessary to remember the formulas; the whole calculation becomes a matter of only a few seconds, and is purely mechanical. It is the usual form of ten-inch slide-rule, with the addition of certain scales and indices. The manipulation is quite simple and rapid, requiring no knowledge of the mathematical principles involved in the formulas.[1]"

[1] The rule, with directions for use, may be obtained from Keuffel and Esser Co., 127 Fulton Street, New York.

The same rule is adaptable to all problems of multiplication and division, and is of great service in all laboratory calculations.

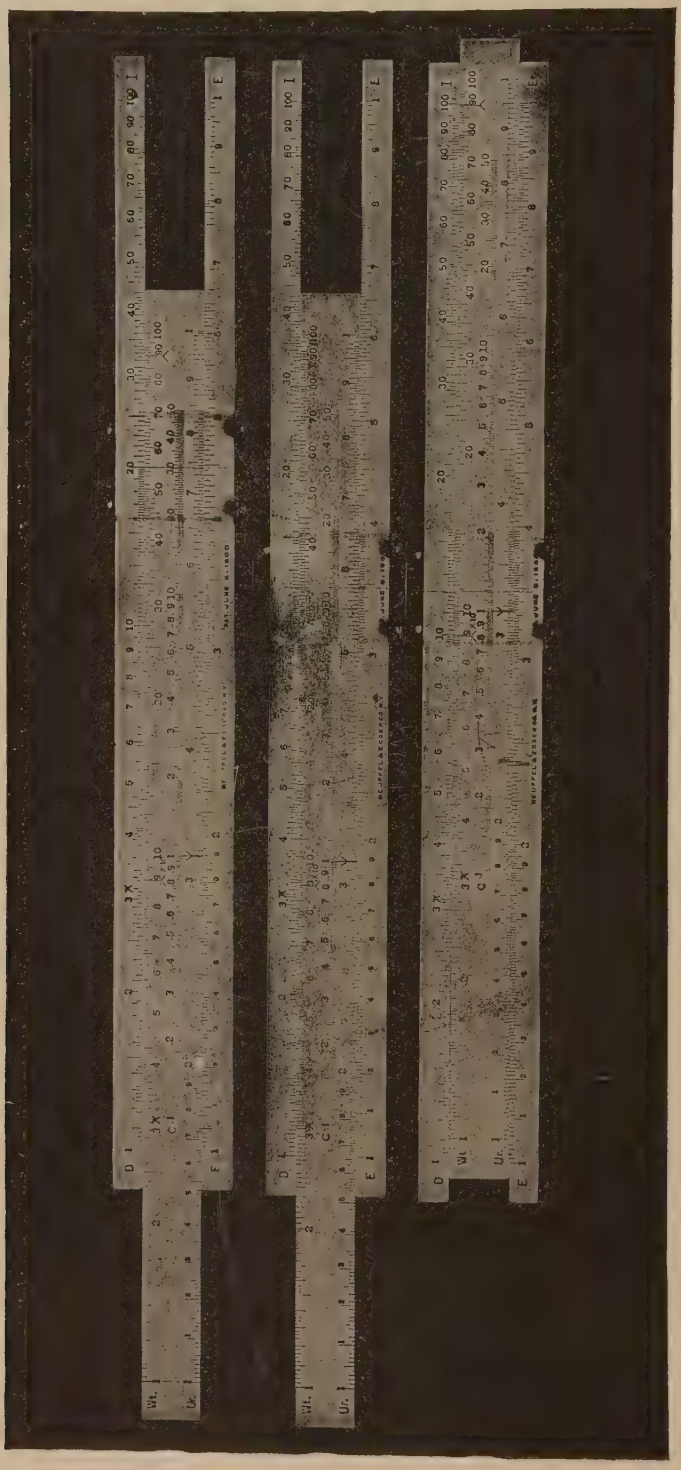

Fig. 458.—Slide-rule for Rapid Calculations. I, II, and III Show the Calculation of McLean's Index of Urea Excretion, with a Slide-rule; Example: Gm. urea excreted per 24 hrs., D = 20.0; Gm. urea per liter of urine, C = 11.0; Gm. urea per liter of blood, Ur = 0.330; Body weight in kilos, Wt = 55.0. I. 55.0 on Wt scale is set opposite 20.0 on D scale (first position). II. Hair line on runner is moved to 11.0 on C scale (second position). III. Slide is moved so that 3.30 on Ur scale is at hair line on runner (third position). Reading is now made at the arrow which points to scale I and is between 99.0 and 100.0. Therefore the index, I, is 100.0. (After McLean, J. Exper. M.)

McLean's studies have led him to the conclusion that, as a rule, increased concentration of urea in the blood is a compensatory phenomenon, "to provide sufficient pressure to cause its excretion through a damaged outlet. Under certain conditions actual accumulation occurs." He finds that the excretion of chlorids and the excretion of urea are functions that may be entirely independent of one another.

According to Widal, Weill and Vallery-Radot, Ambard's constant is somewhat increased in the upright position, and is higher in a person who has been long up and about than just after getting out of bed.

Achard and Leblanc assert that Ambard's constant in convalescence from acute diseases, especially the infectious diseases, is often subnormal, even when there is no oliguria. In such cases, the urea of the blood is often low, and still there is often no parallelism between Ambard's constant and the degree of azotemia. They believe that these variations in the constant are due to extrarenal influences, and that they do not indicate a variation in the permeability of the kidney.

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(*b*) *Simultaneous Studies of Non-nitrogenous Substances in the Blood and in the Urine*

Here, the clinical studies have dealt with (i) the sodium-chlorid content, and (ii) the content in total electrolytes.

i. Determination of the Sodium-Chlorid Content of the Blood and of the Urine

Studies of the sodium chlorid have been made in two directions, (1) the determination of "the NaCl-secretion threshold," and (2) the "NaCl-secretion constant."

Widal, Ambard and Weill (1912) found the threshold for the secretion of NaCl, that is, the concentration of NaCl in the blood plasma necessary to start excretion of NaCl in the urine, to be fairly constant at about 5.62 *g.* per liter. They observed that while excretion of urea occurs no matter how low its concentration in the blood falls, there is a threshold for chlorid excretion, and when the concentration of NaCl in the plasma falls below this threshold value, excretion of chlorid practically ceases.

The *threshold of NaCl-secretion,* according to Ambard, Chabanier and Onell, is not fixed. It varies somewhat in health, and it is much influenced by the administration of drugs and by disease processes. They believe that it represents an important regulatory mechanism for the maintenance of a fairly constant composition of the blood. Their studies indicate that the excretion of water, of sodium chlorid, and of sugar in the urine stand in relation to a definite content of these substances in the blood. With the same concentration of NaCl in the urine, the NaCl-content of the urine increases parallel to the square of the value by which the NaCl-threshold of the blood is exceeded. They have formulated the following law: When the NaCl-threshold-value is exceeded, the NaCl-output in the urine increases in the same way as the reciprocal value of the square root of the NaCl-concentration of the urine. These investigators then calculate *the NaCl-secretion-constant,* a knowledge of which in turn allows them to determine the degree by which the NaCl-threshold is exceeded. Since, however, the *urea-constant* and the *NaCl-secretion-constant* grow in the same relative way, the calculation for NaCl can, they believe, be made from a knowledge of the ureo-secretory constant.

Achard and Ribot made a careful study of NaCl-retention in certain dropsical nephropathies with low NaCl-content in the blood. The increase of the NaCl-secretion-threshold in cases of dropsical renal disease had caused Widal and his associates to refer the NaCl-retention to insufficient renal excretion of NaCl. Achard and Ribot find, however, that the NaCl-secretion-threshold in health, and in disease, is very variable, and that it can be low even in dropsies, despite a low NaCl-content of the blood. They conclude, therefore, that the slight retention in the dropsical nephropathies may be entirely independent of any defect in NaCl-elimination. They do not think that the calculation of the threshold-value has any clinical significance, because it makes the mistake of starting with the assumption that constant relations exist. They assert that the calculation of the NaCl-threshold gives us no clue to the NaCl-permeability of the kidney, nor to the degree of a slight retention.

This subject has become of renewed interest to American investigators, since McLean at the Hospital of the Rockefeller Institute has subjected the matter to control with the use of very accurate methods of determination of NaCl in the urine and in the blood-plasma.

McLean finds that the "normal and usual range of concentration of chlorids in human plasma is from 5.62 to 6.25 grams of sodium chlorid per liter or higher, according to the amount ingested. On the excess over a threshold of about 5.62 grams per liter depends the rate of excretion, the laws governing which can be expressed numerically.

The law of excretion for NaCl, set up by Ambard and Weill, is as follows (I quote from McLean's article):

$$\frac{\text{Excess NaCl over 5.62 gm. per liter of plasma}}{\sqrt{\frac{\text{NaCl in 24 hrs.}}{\text{Wt. in kilos}}}\sqrt{\text{NaCl per liter of urine}}} = \text{Constant.}$$

For *practical use* it appears best to *calculate the plasma sodium chlorid from the rate of excretion,* and to compare the calculated concentration with that actually found. The formula, as derived with the use of values actually found for the constant in the above formula, reads

$$\text{Plasma NaCl} = 5.62 + \sqrt{\frac{D \times \frac{70}{Wt}\sqrt{\frac{C}{14}}}{79.33}}$$

(The symbols have the same meaning as in the urea formulas.)
This, in its simplest form, reads

$$\text{Calculated plasma NaCl} = 5.62 + \sqrt{\frac{\text{Gm. NaCl per 24 hrs.} \sqrt{\text{Gm. NaCl per liter of urine}}}{4.23 \times \text{Wt. in kilos}}}$$

McLean's studies on the NaCl-content of the urine and of the blood, and his calculations of the rate of excretion of NaCl and of the threshold-value of NaCl have convinced him of the following:

1. Relatively increased concentration of chlorids in the plasma occurs in certain conditions, especially in certain forms of cardiac and renal disease.
2. Under certain conditions, notably in fevers or in diabetes, or by the action of diuretics (digitalis), the chlorid threshold may be temporarily or permanently lowered. This may result in a decrease in the concentration of chlorids in the plasma to a point lower than the lowest point that is seen in normals.
3. Failure to excrete chlorids in pneumonia is associated with a lowered concentration of chlorids in the plasma. Excretion begins at the time this concentration increases.
4. Edema is usually accompanied by a relatively increased concentration of chlorids in the plasma. The relations ordinarily return to the normal state when edema disappears.
5. Chlorid and urea functions may be quite independent of one another.

ii. Determination of the Total Electrolytes of the Blood and of the Urine (Hemorenal Index)

These have been studied especially by R. Bromberg, who makes use of what he calls a *hemorenal index,* which he regards as important for diagnosis and prognosis.

By the hemorenal index, he means the relation of the concentration of total electrolytes in the urine to that in the blood. Normally this relation is as 2:1, and the hemorenal index = 2. He asserts that in renal disease, at the beginning, the excretion of electrolytes is the first thing to be disturbed, and that it is only later that the excretion of nitrogenous substances becomes involved. A low hemorenal index, therefore, indicates beginning renal insufficiency. He believes that the method is especially useful for the diagnosis of unilateral disease of the kidney, by comparing the urines obtained from each kidney by ureteral catheterization. He

makes use of an apparatus by which the concentration of the blood stream, on the one hand, and of the urine, on the other, in electrolytes, is measured by the resistance offered to electrical conductivity.

In a later paper, he states that ureteral catheterization is superfluous, that when his hemorenal index = 2, the kidneys are either healthy, or only one of them is diseased; the latter point can be decided by cystoscopy, or by chromocystoscopy. If the index is less than 2, bilateral disease of the kidneys exists. If the index is less than 1.5, whatever condition exists is inoperable.

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(c) *Simultaneous Determination of Both Nitrogenous and Non-Nitrogenous Substances in the Blood and in the Urine*

We now come to some of the more recent methods of studying renal function.

i. Determination of the Total Nitrogen and of the Total Chlorids in the Blood and in the Urine, and Their Concentration-Relations

In 1914, Hefter and Siebeck published an important paper bearing upon the concentration-relations of N and Cl, in health, and in the nephropathies. The most important work of the kidney is to excrete a fluid that is more concentrated in certain substances than is the blood. In their studies, they tested the capacity of the kidney to excrete urines of maximal concentration, and by studying the serum and urine simul-

taneously, they got at the concentration-relations of the two fluids. It is not enough to determine alterations in total concentration, for the kidney may, in its work, either concentrate, or dilute, when single substances are considered. Since the nitrogenous substances and the chlorids are the most important, they were made the object of especial study.

Hefter and Siebeck place the patient, for several days before the test is made, upon a diet that has a low content in both N and Cl. They take blood and urine for examination, in the first place, in the early morning (fasting), and other specimens four hours after a meal rich in N and in NaCl, with limitation of fluid, and then examine the concentration-relations of N and of Cl. This is their so-called "*concentration experiment.*" Next, they make a so-called "*dilution experiment,*" in which they study the concentration-relations 1-1½ hours after the person has swallowed 1½-2 *l.* fluid.

They determine the *nitrogen* in the urine and the *rest-nitrogen* of the blood by the colorimetric method of Folin; the *chlorids* are determined by Volhard's method. They also make use of *cryoscopy.* They express their results in *mgr.* of N, or of Cl, in 100 *c.c.*

Their actual findings were as follows:

A. Healthy Adult. (1) *Fasting:* N-concentration in the urine : N-concentration in the serum :: 20-40 : 1.

Cl-concentration in the urine : Cl-concentration in the serum :: 1.4-2 : 1.

(2) *Concentration test:* N in serum : N in urine :: up to 50 : 1.

Cl in serum : Cl in urine :: up to 4 : 1.

(3) *Dilution test:* N in serum : N in urine :: 3-7 : 1. Cl in serum : Cl in urine :: 0.2-0.5 : 1.

B. Nephropathic Adult with Hyposthenuria and Uremia. (1) *Fasting:* the nitrogen-relation was often as low as 3–10 : 1. The chlorin-relation was often under 1.

(2) *Concentration test:* the N-relation was still lower. The Cl-relation was not changed by the concentration test, even though the Cl of the blood was not increased.

C. Milder Cases of Nephropathy.—In these, they found the N-relation 10–20 : 1.

D. Cases of Arterial Hypertension.—In these, they often found the N-relation normal, both on fasting and on making the concentration experiment.

ii. Determination of the N and the Cl of the Blood and of the Urine in Association with the Following of the Excretion of Water and the Specific Gravity of the Urine After a Renal Test Diet

We now come to one of the most important clinical methods of studying renal function. The *food-* and the *fluid-intake* are strictly controlled by the use of a *renal test diet.* The *water-output* in the urine is exactly measured every two hours; and the *specific gravity* of the urine is closely followed in order to determine the presence or absence of an hyposthenuria. At the same time, the *nitrogen* and the *chlorids* of the blood

and of the urine are determined in order that the concentration-relations of each may be established.

Hedinger and Schlayer (1914) make use of a special renal test diet, chosen for the purpose of seeing how the kidney will behave under slight strain. This diet is chosen so that it will do no harm, though it puts temporarily some work on the kidney. This method, somewhat modified, is now being used by Dr. H. O. Mosenthal in Janeway's clinic at the Johns Hopkins Hospital, and it has been found to yield exceedingly interesting and important results for diagnosis and for prognosis. The renal test diet is given in the following table:

RENAL TEST DIET

For ..... Date .....

All food is to be *salt free* food from the diet kitchen.

Salt for each meal will be furnished in weighed amounts.

All food or fluid not taken must be weighed or measured after meals and charted in the spaces below.

Allow no food or fluid of any kind except at meal times.

Note any mishaps or irregularities that occur in giving the diet or collecting the specimens.

Breakfast, 8 A. M.

Boiled oatmeal—100 *g.*		.....
Sugar—1–2 teaspoonfuls		.....
Milk—30 *c.c.*		.....
2 slices bread (30 *g.* each)		.....
Butter—20 *g.*		.....
Coffee—160 *c.c.*	200 *c.c.*	.....
Sugar—1 teaspoonful		.....
Milk—40 *c.c.*		.....
Milk—200 *c.c.*		.....
Water—200 *c.c.*		.....

Dinner, 12 Noon.

Meat soup—180 *c.c.*		.....
Beefsteak—100 *g.*		.....
Potato (baked, mashed or boiled)—130 *g.*		.....
Green vegetables, as desired		.....
2 slices bread (30 *g.* each)		.....
Butter—20 *g.*		.....
Tea—180 *c.c.*	200 *c.c.*	.....
Sugar—1 teaspoonful		.....
Milk—20 *c.c.*		.....
Water—250 c.c.		.....
Pudding (tapioca or rice)—110 *g.*		.....

Supper, 5 P. M.

Two eggs, cooked in any style	.....
Two slices bread (30 *g.* each)	.....
Butter—20 *g.*	.....
Tea—180 *c.c.*	.....
Sugar—1 teaspoonful } 200 *c.c.*	.....
Milk—20 *c.c.*	.....
Fruit (stewed or fresh)—1 portion	.....
Water—300 *c.c.*	.....

8 A. M. No food or fluid is to be given during the night or until 8 o'clock the next morning (after voiding), when the regular diet is resumed.

Patient is to empty bladder at 8 A. M. and at the end of each period, as indicated below. The specimens are to be collected for the following periods in properly labeled bottles, to be furnished by the Chemical Division of the Medical Clinic.

8 A. M.–10 A. M.; 10 A. M.–12 N.; 12 N.–2 P. M.; 2 P. M.–4 P. M.; 4 P. M.–6 P. M.; 6 P. M.–8 P. M.; 8 P. M.–8 A. M.

Specimens are to be left in ward until called for at 8:30 A. M. by attendant from the Chemical Laboratory.

The results are recorded according to the following schedule:

DATA AFTER RENAL TEST DIET

Name..... Date.....

Time of Day	Urine		NaCl		N		Time and c.c. of Fluid Intake
	c.c.	Sp. G.	Per Cent	Gms.	Per Cent	Gms.	
8–10	....	....	....	....	....	....	....
10–12	....	....	....	....	....	....	....
12– 2	....	....	....	....	....	....	....
2– 4	....	....	....	....	....	....	....
4– 6	....	....	....	....	....	....	....
6– 8	....	....	....	....	....	....	....
Total, Day	....	....	....	....	....	....	....
Night, 8–8	....	....	....	....	....	....	....
Total, 24 Hours	....	....	....	....	....	....	....
Intake	....	....	....	....	....	....	....
Difference	....	....	....	....	....	....	....

Impression:

Hedinger and Schlayer found that, in normal individuals their test diet was followed by an increased quantity of urine, a lowering of the specific gravity, and a lowering of the sodium-chlorid concentration of the urine after the diet, though the diuretic effect may come very quickly or more slowly in different persons. In 30 patients suffering from renal disease, however, they were struck by the absence of marked variation in the specific gravity and in the NaCl-concentration of the urine after the diet. Moreover, the water-output varied but little. This type of hyposthenuria was found, not only in some cases of nephritis, but also, sometimes, in pyelitis, in renal tuberculosis, and in stasis kidney. In very mild cases of nephritis, the flattening of the curves expresses itself usually in a constancy of the specific gravity in the afternoon or in the early evening hours.

Dr. Mosenthal has kindly given me the protocols of studies made by him in three cases in the Johns Hopkins Hospital: (1) a *normal person,* (2) a case of *marked hypertensive nephropathy,* and (3) a case of aortic insufficiency with *marked cardiac decompensation.* The protocols are here reproduced, as they illustrate well the findings in three different types of cases, and the value of studies in association with the use of a renal test diet.

I. Protocol of Normal Person

Time of Day	Urine		NaCl		N	
	c.c.	Sp. G.	Per Cent	Gms.	Per Cent	Gms.
8–10	153	1.016	1.32	2.02	.89	1.26
10–12	156	1.019	1.25	1.95	.74	1.15
12– 2	194	1.012	.64	1.24	.59	1.14
2– 4	260	1.014	.77	2.00	.56	1.46
4– 6	114	1.020	.99	1.13	.95	1.08
6– 8	238	1.010	.43	1.02	.52	1.23
Total, Day	1115	.....	....	9.36	....	7.32
Night, 8–8	375	1.020	.63	2.36	1.23	4.61
Total, 24 Hours	1490	.....	....	11.72	....	11.93
Intake of Fluid, NaCl and N.	1760	.....	....	8.5	....	13.4
Difference	+270	.....	....	=3.22	....	+1.47

Impression: Normal case. Note the variations in specific gravity from 1.010 to 1.020, the irregular output of fluid in the two-hourly specimens, the polyuria being most marked after meals, the low quantity of urine at night (less than 400 c.c.), the high specific gravity in the night urine and the high concentration of nitrogen in the night urine. The total outputs of water, salt and nitrogen are approximately normal, as compared with the intake.

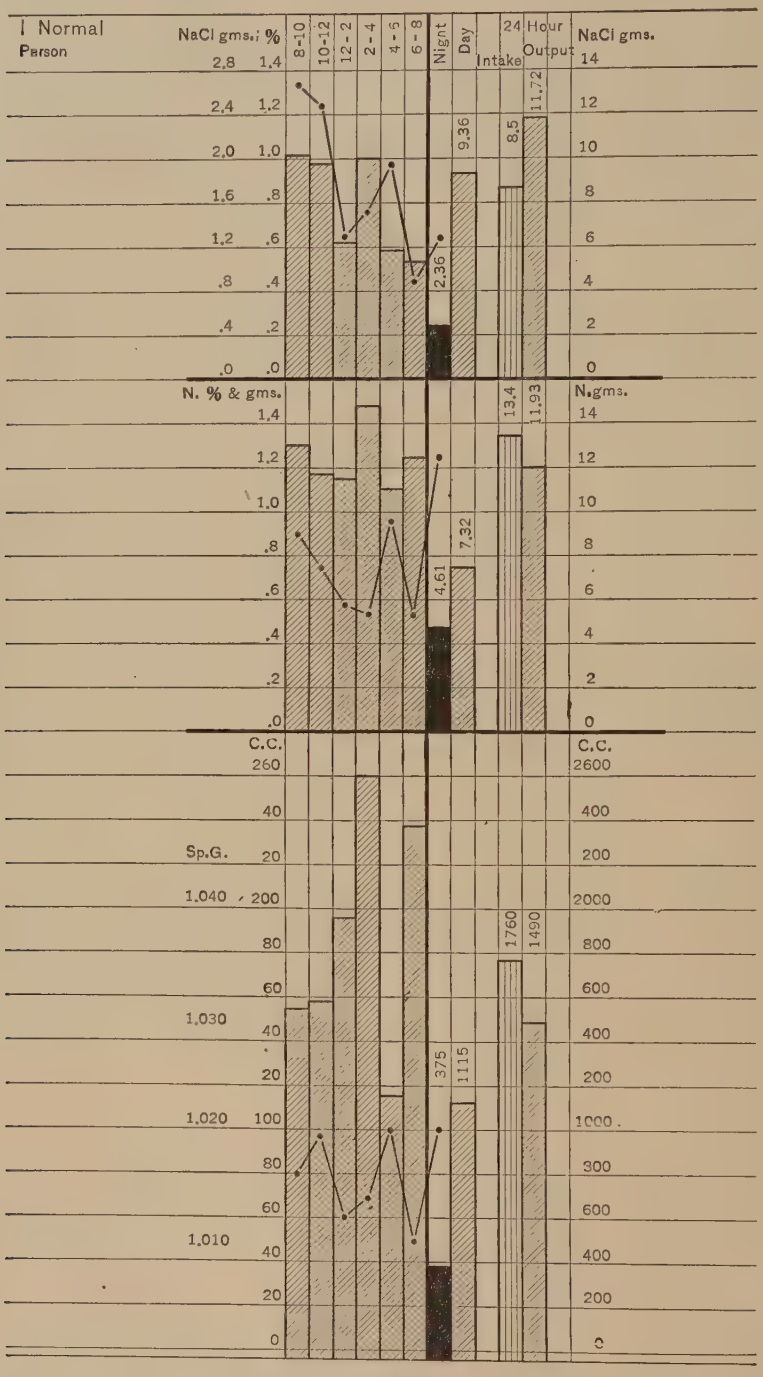

Fig. 459.—Water Intake, Water Output, Specific Gravity, NaCl Intake and NaCl Output, Nitrogen Intake and Nitrogen Output, in a Normal Person.

II. Protocol in a Case of Hypertensive Nephropathy

Mrs. B. B.; age, 32; white; housewife.

Complains of weakness and nervousness, and has recently had several convulsive seizures. The blood pressure, systolic, is 230, diastolic, 140 mm. of mercury. There is slight thickening of the peripheral arteries; the phenolsulphonephthalein output is 5 per cent in two hours; urine is low in specific gravity, averaging about 1.010; there are 2 to 3 grams of albumin per liter, and, on microscopic examination, a few hyaline and granular casts. The non-protein nitrogen of the blood is 83 mgms. per 100 c.c., and there is a considerable degree of albuminuric retinitis, arteriosclerosis, hypertension, contraction of the kidneys (chronic interstitial change) and uremia.

Time of Day	Urine		NaCl		N	
	c.c.	Sp. G.	Per Cent	Gms.	Per Cent	Gms.
8–10	133	1.010	.36	.48	.33	.47
10–12	176	1.009	.36	.63	.34	.60
12– 2	156	1.010	.32	.50	.35	.55
2– 4	212	1.009	.36	.76	.34	.72
4– 6	164	1.009	.38	.62	.36	.59
6– 8	104	1.010	.33	.34	.33	.34
Total, Day	945	.....	....	3.33	....	3.27
Night, 8–8	590	1.009	.34	2.01	.38	2.24
Total, 24 Hours	1535	.....	....	5.34	....	6.51
Intake of Fluid, NaCl and N	1510	.....	....	5.8	....	12.2
Difference	−25	.....	....	+.46	....	+5.69

Impression: Hypertensive nephropathy of marked degree. Note the fixation of the specific gravity (1.009-1.010), the increase of urine at night, the low specific gravity and the low concentration of nitrogen in the night urine. The percentage of salt and nitrogen in the two-hourly specimens is remarkably fixed, in contrast to the variations seen in the normal case. The total output of nitrogen and salt is much diminished. Renal function is very markedly impaired.

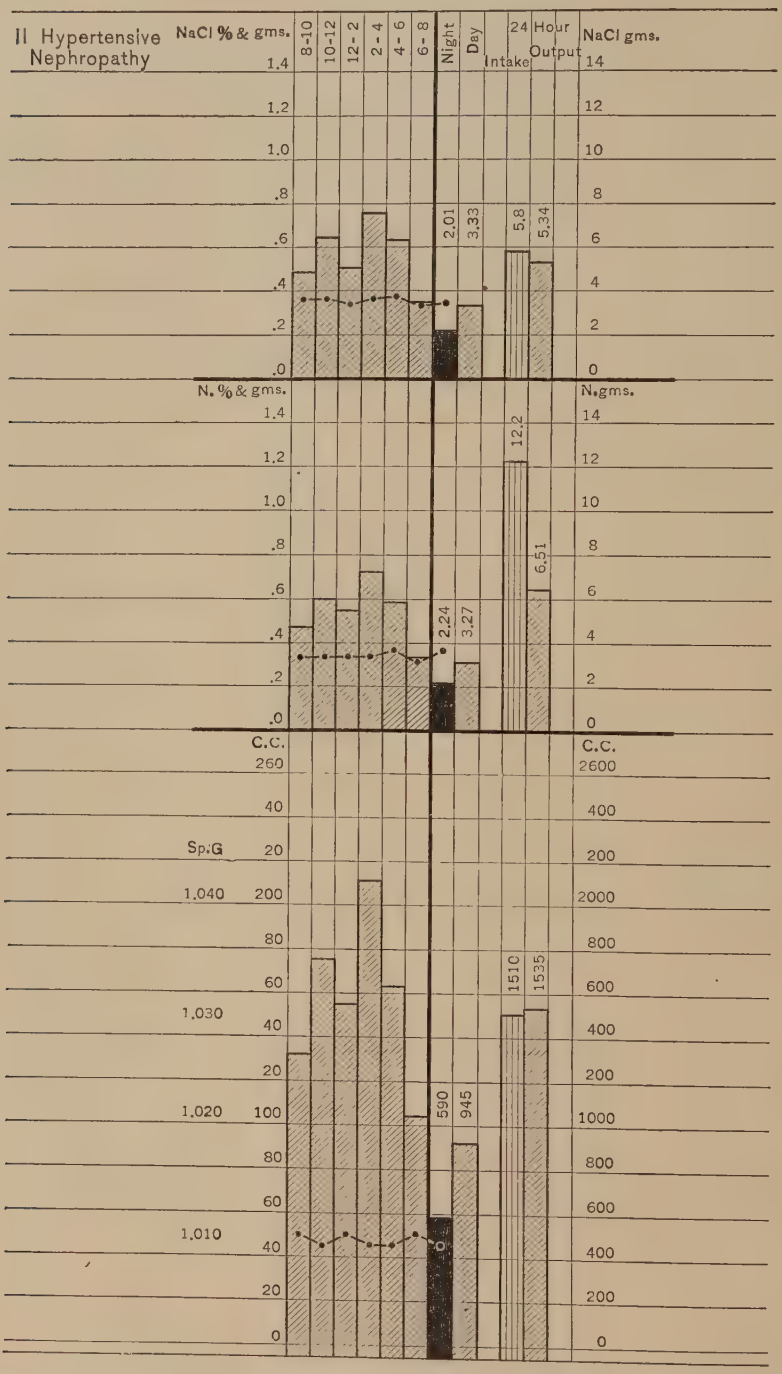

Fig. 460.—Water Intake, Water Output, Specific Gravity, NaCl Intake NaCl Output, Nitrogen Intake and Nitrogen Output, in a Patient Suffering from Hypertensive Nephropathy.

III. Protocol in a Case of Aortic Insufficiency, with Marked Myocardial Decompensation (General Anasarca)

Time of Day	Urine		NaCl		N	
	c.c.	Sp. G.	Per Cent	Gms.	Per Cent	Gms.
8–10	61	1.018	.20	.12	1.52	.93
10–12	52	1.020	.24	.12	1.83	.95
12– 2	65	1.019	.26	.17	1.73	1.12
2– 4	55	1.018	.27	.15	1.65	.90
4– 6	30	1.020	.26	.07	1.61	.48
6– 8	35	1.021	.40	.14	1.80	.63
Total, Day	298	.....	....	.77	....	5.01
Night, 8–8	275	.....	....	.85	....	5.07
Total, 24 Hours	573	.....	....	1.62	....	10.08
Intake of Fluid, NaCl and N	570	.....	....	6.50	....	11.00
Difference	−3	.....	....	+4.88	....	+.92

Impression: Marked myocardial decompensation and passive congestion of the kidney. In this case, the very low concentration of chlorids and high concentration of nitrogen, the oliguria, accompanied by a high fixed specific gravity, are very characteristic of congestion of the kidney (stasis kidney). The height of the specific gravity and the very large amounts of nitrogen put out readily distinguish this condition from that of hypertensive nephropathy.

If, in association with the following of the water-excretion and the specific gravity of the urine after the renal test diet, we combine simultaneous examination of the nitrogen (non-protein nitrogen; urea-nitrogen) and the chlorids, of the blood and of the urine, with determination of Ambard's coefficient, and if we utilize, also, the phenolsulphonephthalein test, and, perhaps, the lactose test, we have very satisfactory methods indeed of informing ourselves regarding the functional efficiency of the kidneys.

If the general practitioner should be unable to make the chemical determinations of the blood and urine just referred to, or should he not be in a position to have them made for him, he will be surprised at the valuable information he can gain simply from (a) the use of the renal test diet, followed by (b) a comparison of the water-intake and the water-output, and (c) the careful determination of the specific gravity of each two-hourly period of urine, and (d) the use of the phenol-sulphonephthalein test.

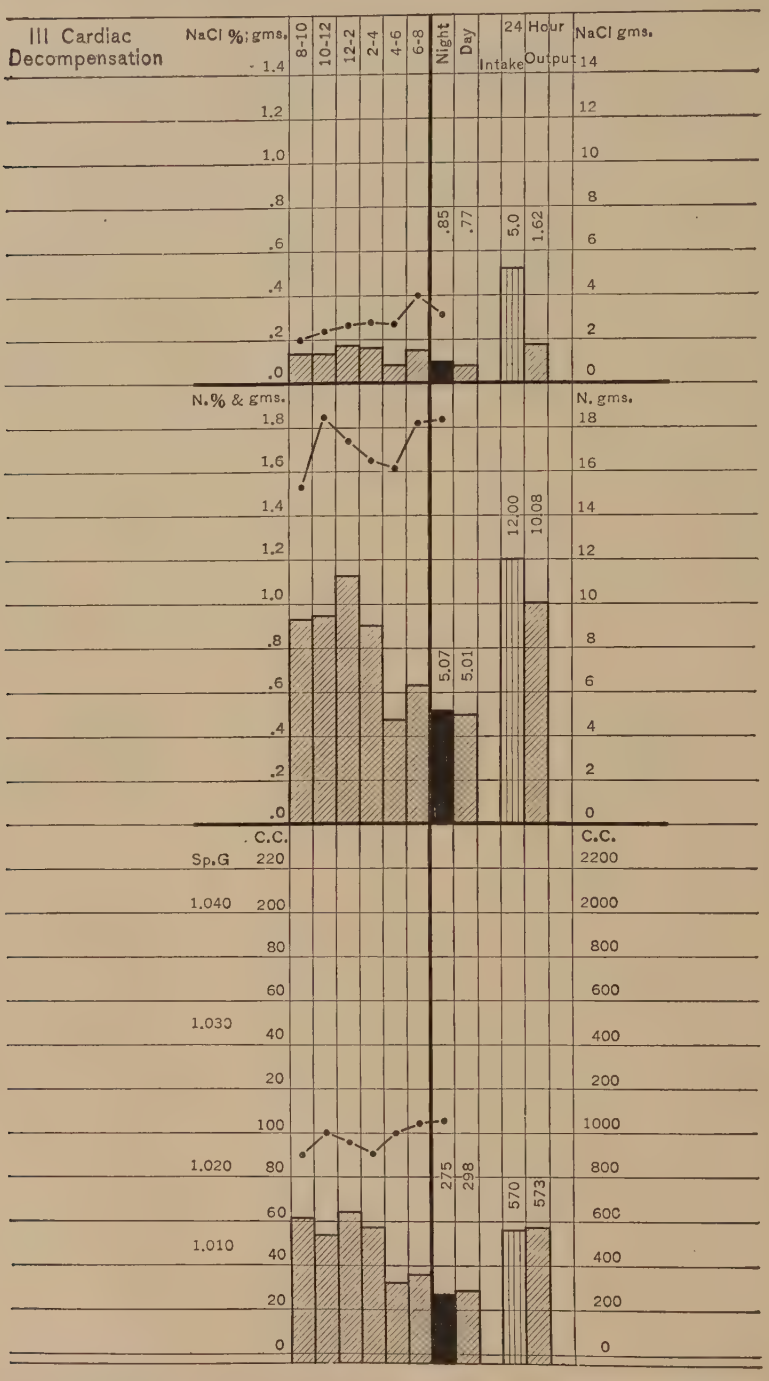

Fig. 461.—Water Intake, Water Output, Specific Gravity, NaCl Intake, NaCl Output, Nitrogen Intake and Nitrogen Output, in a Patient Suffering from Cardiac Decompensation.

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5. Other Methods for Testing the Functional Capacity of the Kidneys

We may mention, briefly, four or five other methods that have been employed.

(*a*) *Determination of the Capacity to Secrete the Toxic Substances of Normal Urine* (*Bouchard's Urotoxic Coefficient*)

The nature of the poisons concerned has been much discussed. Many believe them to be potassium salts, but probably other poisons are also active.

This is a biological test, introduced by Bouchard, for judging of the excretory power of the kidneys. It depends upon the determination of the amount of urine from the patient necessary to kill a rabbit. The toxic effect is expressed per kilogram of body weight of the rabbit. In renal disease, the kidneys do not excrete these toxic substances in normal amounts, and more urine is required as a lethal dose than from healthy individuals.

(*b*) *Determination of the Urea-Content of the Cerebrospinal Fluid*

Soper and Granat have made careful studies of the urea-content of the cerebrospinal fluid. They examined 56 cases without renal disease, 21 cases of fatal uremia, and 8 cases of non-fatal renal disease. Their conclusions were as follows: A urea-content of more than 0.2 per cent indicates severe uremia and a quickly fatal result; a urea-content of 0.1–0.2 per cent in most renal diseases is a grave sign, and is likely to be followed by uremia; when the content is 0.05–0.1 per cent, no diagnostic or prognostic conclusions may be drawn.

(*c*) *Determination of the Fatigability of the Excretory Power of the Kidney*

Mosenthal and Schlayer have made a careful study of the fatigability of the kidney in disease. They found that the kidney may show signs of fatigue in

different ways. The kind of diuretic that fatigues the kidney depends upon the functional state of the organ, and upon the kind and number of the preceding stimuli that have acted upon it. They studied, especially, the effects of sodium chlorid and of caffein.

P. von Monakow has studied the fatigability after the administration of diuretin, theocin and urea.

Only a beginning in such studies has been made, but the results indicate that fruitful work may be done along this line, and that clues for therapy may be thus obtainable.

(*d*) *Determinations Bearing Upon the Acidity of the Blood in Renal Disease, and Upon Alkali Retention by the Kidneys*

Under this heading, two recent methods of examination may be mentioned: (i) the measurement of the CO_2 tension of the blood, and (ii) determination of the amount of sodium bicarbonate necessary to render the urine alkaline.

i. Measurement of the CO_2 Tension of the Blood

Porges and Leimdorfer have studied the CO_2 tension of the blood in renal dyspnea, and believe that it gives a clue to the degree of renal insufficiency. As is well known, the CO_2 tension of the blood is a guide to acidosis. We have now many methods of studying the degree of acidosis. Probably the new method of Levy, Rowntree and Marriott (see Part VII) for determining the hydrogen-ion content of the blood may prove to be the easiest method for the purpose. The studies of the acidosis of dyspnea by G. F. Peabody, F. McPhedran, T. Lewis and others are all interesting in this connection.

ii. Determination of the Amount of $NaHCO_3$ Necessary to Render the Urine Alkaline

On a number of my own patients, Dr. A. W. Sellards has made a series of observations to determine how much $NaHCO_3$, given by intravenous injection, is necessary to render the urine alkaline. The quantity in health is fairly constant, whereas in the nephropathies enormous amounts may be required. In how far this depends upon an acidosis, and in how far upon an inability of the alkali to pass through the renal filter, we do not know. The studies of Palmer and Henderson on acid-base equilibrium are interesting in this connection, as are also the monographs of Martin H. Fischer on nephritis and on edema.

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6. Methods for Determining the Functional Capacity of Each Kidney Separately, and of Comparing the Functional Efficiency of One Kidney with that of the Other

By means of *ureteral catheterization* (*q. v.*), the urine from each kidney can be collected separately and so the amounts of urine, and also the solid substances, excreted by each during a given time can be compared (M. Nitze, H. A. Kelly, Albarran, Caspar and Richter). The procedure is of especial value in *surgical cases* in which one kidney is so seriously diseased as to demand nephrectomy. Before performing nephrectomy, however, the surgeon desires to assure himself (1) that *the other kidney is present*, and (2) that *the other kidney is still healthy enough to keep the patient alive.*

In *collecting the urine* in such cases, the ureteral catheters must remain in place long enough to secure enough urine for examination and to permit of the application of certain functional tests.

In a thorough examination we may measure (1) the *amount* of urine, (2) the *acidity*, (3) the *specific gravity*, (4) the *nitrogen-output*, (5) the *molecular concentration* = $\triangle$ (cryoscopy), (6) the *ion-content* (electrical conductivity), (7) the *sodium-chlorid content* and (8) the *phenolsulphonephthalein-output* of each kidney after intramuscular injection of a given amount of this chemical; in some cases .01 gram of phloridzin is injected subcutaneously and the amount of sugar excreted by each kidney subsequently determined.

The *reaction* and the *degree of acidity* are often helpful in giving clues regarding the character of bacteria causing an infection (acid-producers, alkali-producers). Moreover, there is a form of urinary hyperacidity of neuropathic origin, in which there is no infection, though the symptoms may simulate those of cystitis (T. R. Brown). In normal persons, using phenolphthalein as indicator, about 2.5 c.c. of N/10 NaOH are required to neutralize 10 c.c. of urine.

From the *specific gravity* we gain information regarding the concentration or the dilution of the urine on each side; in unilateral nephritis,

there may be a marked difference between the two sides. In pyelitis and in pyelonephritis, a low specific gravity is often observable.

The amount of *albumin* if any is present and the formed elements on *microscopic examination* (casts, red blood cells, pus cells, crystals) may be compared on the two sides. *Smears, bacterial cultures* (aerobic and anaerobic), and *animal inoculations* from the urine of each side may be made. A careful search for *tubercle bacilli* is often of great diagnostic importance.

When one kidney is diseased, the absolute amounts of *nitrogen*, of *chlorids*, and of *sugar* (*after phloridzin*) excreted are diminished, and the *molecular concentration* is low.

In the following example, the value of the method is illustrated. A patient who consulted me in March, 1912, complaining of nervousness and depression, and giving a history of an abscess in the right flank after typhoid fever some years before, was found to have albumin and great numbers of motile bacilli in his urine. At my request, Dr. J. T. Geraghty catheterized the ureters with the following results:

First Period

Urine	Right Kidney	Left Kidney
Amount	6 c.c.	40 c.c.
Urea	0.3 per cent	0.3 per cent
Time of first appearance in the urine of the phthalein after injection	8 min.	3 min.
Amount of phthalein excreted	2 per cent	30 per cent
Chemical and microscopic examination	Albumin, pus cells and bacilli present.	Normal urine except for trace of albumin.

Second Period

Urine	Right Kidney	Left Kidney
Amount	10 c.c.	55 c.c.
Urea	0.25 per cent	0.2 per cent
Amount of phthalein excreted	2.5 per cent	10 per cent

Conclusion: Chronic infection of the right kidney with marked reduction of functional efficiency. Compensatory hypertrophy of the left kidney with (probably) a slight toxic nephropathy, secondary to the disease of the right kidney. A

pure culture of the *colon bacillus* grew from the urine from the right kidney; no tubercle bacilli were present.

Another example of functional renal diagnosis may be cited (after Casper):

Normal Case			Pathological Case (Tuberculosis of the Left Kidney)		
Urine	R.	L.	Urine	R.	L.
Amount	36 cm.³	35 cm.³	Amount	16 cm.³	10 cm.³
△	0.50	0.50	△	1.5	0.91
Sugar	1.4 per cent	1.4 per cent	Sugar	2.0	0.05
N	0.213	0.206	N	0.63	0.385

Such comparative tests, dependent as they are upon ureteral catheterization, can be made only by specialists, as the technic of ureteral catheterization is too difficult for the general practitioner, who needs to make use of it only occasionally, to apply. It is likely, therefore, to remain in the hands of men who devote themselves to the urogenital specialty. Collection by segregators is not reliable. In a few urgent cases, it may be necessary and justifiable, if it be impossible to catheterize the ureters in the ordinary way, to open the bladder by suprapubic cystotomy and then to introduce urethral catheters, when if one kidney be sound the other diseased kidney may be removed.

We must not lose sight of the fact that the catheterization of the ureter may, in itself, reflexly disturb urinary secretion; the catheters should be left in until such reflex disturbances pass off.

The *sugar test* (with phloridzin) appears to be rather unreliable since normal kidneys may vary in their response to it. A pathological kidney may excrete sugar earlier than a healthy kidney.

In the comparative tests, we rely mainly upon the findings as regards albumin, casts, blood, pus, bacteria and phenolsulphonephthalein excretion. The other tests above mentioned, as well as the time of excretion of methylene blue and indigosulphate of carmin are less helpful.

F. Examination of the Urinary Passages

1. Examination of the Ureters

In the female, the ureters are accessible to *palpation* through the vagina, and the rectum.

It is rarely possible to *feel* the ureters when they are normal, but

if a ureter be thickened or dilated (tuberculosis, ureteritis, stone), its lower part may become palpable through the rectum or the vagina.

When palpating through the vagina, one first ascertains the position of the bladder by means of one hand placed on the abdominal wall, and then feels for the dilated ureteral cords extending from the position of the internal ureteral orifices around the pelvic wall to the site of the cervix in the lateral fornix, above. Occasionally, the normal ureters are palpable as small, freely movable cords (H. A. Kelly). Any *enlargement, thickening*, or *irregularity,* indicates disease of the ureter.

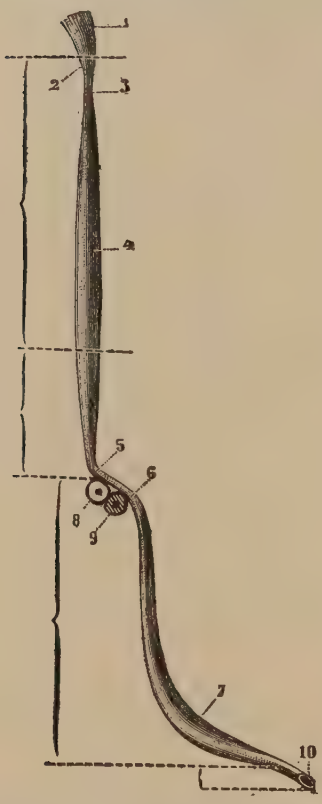

Fig. 462.—Shape of the Right Ureter After It Has Been Injected with Tallow. (Testut.) 1, Pelvis of Kidney. 2, Infundibulum. 3, Narrowing. 4, Wide or Abdominal Portion. 5, Bend at Pelvic Brim. 6, Narrowing at Brim. 7, Widening in Pelvic Portion. 8, 9, External Iliac Artery and Vein. 10, Vesical Orifice. (After R. Guiteras.)

Most diseases of the ureter are secondary to disease of the bladder or of the kidney. The predilection sites for *ureteral stones* are (1) the intravesical portion of the ureter, (2) a point in the lower third of the ureter in front of the sacrum, and (3) the junction of the renal pelvis with the ureter.

In ureteral disease, patients often complain of *colicky pains* along the course of the tube and of changes in the appearance of the urine. If a ureteral *fistula* be suspected, methylene blue may be injected subcutaneously and colored urine will flow through the fistula.

Stones in the ureter can be localized by (1) *x-ray examinations,* (2) by *passage of a wax-tipped ureteral catheter* (Kelly).

Ureteral *catheterization* is made in connection with the cystoscopic examination (see below).

2. Examination of the Urinary Bladder

On examining the *bladder,* we make use chiefly of (1) inspection, palpation and percussion of the suprapubic region, (2) examination of the urine, (3) the internal examination of the bladder by catheterization, sounding, and cystoscopy, and (4) x-ray examinations.

(a) *Inspection, Palpation and Percussion of the Suprapubic Region*

The bladder lies in the true pelvis and, when empty, is entirely behind the symphysis pubis. As it fills with urine, it rises out of the

pelvis above the symphysis, and when much distended gives rise to a smooth spherical swelling in the hypogastrium. In *extreme retention* of urine, it may extend above the umbilicus, become easily palpable and, often, distinctly visible. On percussion, such a tumor yields dullness, convex above, where it is bounded by intestinal tympany. A gravid uterus, an ovarian cyst, or a mesenteric cyst can yield a similar dullness, but *a dullness due to the distended bladder disappears on removing the urine by the passage of a catheter.* Comatose or delirious patients should be carefully watched for distention of the bladder.

Tumors of the bladder, and large *stones* in the bladder, can often be felt on bimanual palpation (one hand on the abdomen, the other in the rectum or in the vagina).

(*b*) *The Examination of the Urine in Diseases of the Bladder*

Albuminuria, hematuria, pyuria or *bacteriuria* may be met with in disease of the bladder.

As a rule, a *pure cystitis* gives rise to but little **albuminuria** if the urine be filtered and examined when freshly drawn; in *pyelitis* and in *pyelonephritis* there is more. When **pyuria** exists, an outspoken disproportion between the amount of pus present and the amount of albumen is in favor of a diagnosis of cystitis, while if there be a marked albuminuria, the pyuria may be due either to pyelitis alone, or to pyelitis and cystitis together. According to Rosenfeld, the albumin-content of the urine in pure cystitis does not exceed 0.1-0.15 per cent, while in pyelitis it is often as high as 0.3 per cent. According to Goldberg, in a combined **hematuria** and albuminuria, if the percentage of albumin present stand to the number of red blood corpuscles per c. mm. of urine in a ratio greater than 1 : 30,000, albumin not accounted for by the blood is present, while if the ratio be less, the albumin present is accounted for by the blood alone.

The only sure way of getting at the *origin of a hematuria* is to resort to cystoscopy and ureteral catheterization. The same may be said of pyuria.

In **bacteriuria,** the microörganisms present may be identified by bacteriodiagnostic methods (stained smears, aërobic and anaërobic cultures, animal inoculations). In ACUTE CYSTITIS, the bacteria most often causative are (1) *Bacillus coli,* and (2) *Staphylococci;* in CHRONIC CYSTITIS, (1) *Bacillus coli,* (2) *Bacillus tuberculosis,* and (3) *Staphylococci.* In PYELITIS, the two commonest causative bacteria are (1) *Bacillus coli* and (2) *Bacillus tuberculosis.* In typhoid fever, bacilluria due to *Bacillus typhosus* is common. The *Bacillus coli* and the *Bacillus tuberculosis* do not lessen urinary acidity, but rather tend to increase it. Certain bac-

teria, especially *Bacillus proteus vulgaris*, exert a marked alkalinizing effect followed by precipitation of phosphates. Some *Staphylococci* are also alkalinizers, but they are less actively so than bacilli of the proteus group. When both alkalinizers and acidifiers are present in the urine, the reaction may be but little affected. Judgments of urinary reaction to be of any value for diagnosis must be formed from tests made on urine *freshly drawn.*

(c) *Catheterization and Sounding of the Bladder*

Instruments.—The best *bougies* for examining the urethra are made of silk, or of linen, covered with gum, and provided with an olive-tip at one, or at both, ends. It is convenient to have four sizes (between 14 and 26, French scale). Such bougies may not be boiled; they should be kept immersed in 1:1,000 bichlorid. After using, they should be thoroughly cleansed with soap and water.

Sounds are curved, solid, metal instruments, useful for palpatory examination of the urethra and the urinary bladder, and for therapeutic purposes (dilatation of stricture, etc.). They are sterilized by boiling. If a number 28 (French scale) will pass through the male urethra, stricture is ruled out. It is convenient to have at least six such sounds (sizes 20-30, French scale).

Catheters have a similar shape, but are hollow instruments with one or two openings at their vesical ends—the "eyes" of the catheter—which permit the passage of fluids from the bladder, or into it. For the *female* urethra, short glass catheters suffice; for the *male* urethra, long catheters (gum-elastic, rubber) of different caliber, are necessary. Young strongly advises the use of the *coudé* (or elbowed) gum-linen catheter, for with it, "catheterization can be successfully performed without injury in almost all cases of obstruction to urination from prostatic hypertrophy." This catheter should be adopted as the standard catheter for general use; it is far better than the straight rubber catheter so largely employed, though the latter may be necessary in cancer of the prostate. A silver catheter should never be used unless the *coudé* or the rubber catheter has failed to find a passage. In prostatic hypertrophy, a special silver catheter, provided with a large "prostatic curve," may be helpful, or with the two stilets of Guyon, one may give almost any curve desired to a gum or to a rubber catheter.

In severe stricture of the urethra, even small sounds cannot be passed, in which case a trial may be made with a catheter attached to a filiform bougie. The practitioner should always be prepared to aspirate the bladder, in cases of retention in which no instrument can be passed; he may use a sterile needle of small caliber.

The following *list of instruments,* recommended by Dr. H. H. Young, should be in the possession of every general practitioner:

(1) Glass urethral nozzles for antiseptic irrigation of the urethra and bladder.

(2) Sounds for the dilatation of the urethra (Nos. 18, 20, 22, 24, 26, 28, French).

(3) Filiforms, for strictures of small caliber, with screws for attachment to dilating followers (Nos. 10, 14, 18, 22, French).

(4) Catheters: (a) *Coudé* prostatic gum silk catheters, which can be boiled (Porgès). (Nos. 14, 16, 18, French).

(b) Rubber straight Nélaton catheters (Nos. 10, 14, 16, 18, French).

(c) A silver van Buren curved catheter (No. 16, French).

(d) Guyon's stilets, coudé and Benigué curves (to give a proper curve to gum and to rubber catheters).

Technic.—On passing a catheter or a sound, most careful asepsis should be practiced (penis and urethra of patient, instruments, physi-

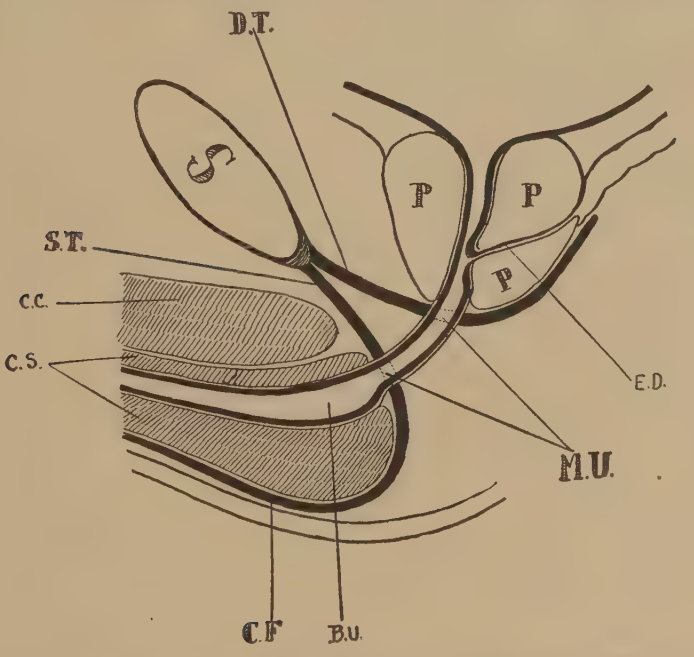

Fig. 463.—Membranous Urethra and Its Relation to the Triangular Ligament. M.U., Limits of Membranous Urethra. D.T., Deep Layer Triangular Ligament. S.T., Superficial Layer of Triangular Ligament. C.C., Corpus cavernosum. C.S., Corpus spongiosum. C.F., Colles' Fascia. B.U., Bulbous Urethra. P., Prostate. E.D., Ejaculatory Duct. S., Symphysis. (After R. Gulteras.)

cian's hands), and the greatest caution in the use of force should be observed. The urethra should be handled with the same delicacy as the eye.

The patient lies with the legs spread apart. In the male, the penis is fixed between the thumb and index finger of the left hand, by which the orifice of the

urethra is also opened. The instrument, held in the right hand, is slowly introduced. If it be a soft instrument, it must be grasped close to the orifice of the urethra. On passing a firmer instrument, held at its distal end between the thumb and index finger of the right hand, the tip of the instrument is placed in the orifice of the urethra, after which the penis is drawn cautiously by the left hand with the greatest delicacy over the instrument as far as possible. The instrument is next introduced to about a rectangular position or a little beyond this, by which time its vesical end is in the bulbus urethrae. By gentle depression of the outer end of the instrument toward the perineum it now passes around the symphysis through the posterior urethra into the bladder, care being taken to let it pass almost by its own weight or at any rate with the use of the least pressure possible. With the *coudé* gum catheter (French make of Porgès), it will be uncommon to experience any difficulty. If it does not pass easily but seems to be caught in the bulbus, it is best to bring it back into its first position and to try again. Once passed, the catheter should be held in position or it may easily slip out.

Before the catheter is withdrawn, the bladder should be irrigated with a 1:60,0000 solution of $HgCl_2$, or with a 1:10,000 solution of $AgNO_3$. For a few days following catheterization hexamethylenamin should be given 3 or 4 times a day, dissolved in a large glass of water. For a few days, the urine should be inspected with the three-glass-test to make sure that no infection has occurred.

Difficulties Sometimes Met with on Catheterization.—Sounding and catheterization may be difficult sometimes, owing to (1) small urethral orifice, (2) catching in the fossa navicularis (usually avoidable by keeping the tip on the upper wall of urethra), (3) cramplike contraction of the external sphincter of bladder (usually overcome by soft constant pressure), (4) enlargement of the prostate (elbowed catheter, prostatic catheter, stiletted and bent catheter), and (5) urethral stricture.

Complications.—Physicians should bear in mind certain complications that sometimes attend instrumental examinations of the urinary passages. Among the more important of these are (1) *syncope*, in nervous individuals, (2) *hemorrhage*, especially in stricture, or in marked hypertrophy of the prostate, (3) *urethral fever* (transitory rigor, and fever soon after the passage of the instrument), (4) the making of a *false passage* (a grave complication due to bad management), and (5) *infection*, for even when an aseptic technic has been employed infection may occur owing to the existence of infectious processes in the urinary passages.

Diagnostic Value.—Catheterization is useful in (1) determining the power of the bladder (amount of residual urine, not exceeding 40 to 50 c.c. normally), (2) the determination of the capacity of the bladder (normally 400 to 500 c.c.), (3) for obtaining samples of urine free from secretions of the urethra for chemical, microscopical and bacteriological examinations.

The sound is useful in diagnosis (1) in demonstrating infiltrations of the urethral wall (chronic gonorrhea), (2) in establishing the site,

form, extent, caliber and hardness of strictures, and (3) for the diagnosis of stone and other foreign bodies in the bladder and urethra.

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[Note.—See also references at beginning of Part X.]

3. Cystoscopy and Ureteral Catheterization

By means of an instrument known as the *cystoscope*, it is possible to inspect the illuminated interior of the bladder (*cystoscopy*).

(*a*) *The Cystoscope*

(a) *The Cystoscope.*—The modern instrument carries an electric light with it into the bladder and also an optical apparatus that greatly enlarges the visual field. Nitze's *simple cystoscope* with the bladder distended with water is much used and is an excellent instrument. It consists of a tube 22 by 25 cm. long, curved at the end (*coudé* beak). It is easy to introduce; and there is but little pain if novocain (5 per cent solution) be used in the urethra. Through a system of lenses, an enlarged picture of a section of the bladder wall can be seen. By changing the position of the instrument the whole bladder wall, and especially the region of the trigone and of the ureteral orifices can be inspected. With this instrument, the diseases of the prostate and the bladder can be easily differentiated from one another, for it permits not only of inspection of the entire bladder, but also of the size and distribution of the lobes of the prostate; moreover, the orifices of the two ureters may be observed, and clues to the condition of each kidney may be gained.

The *orthocystoscope* of E. R. W. Frank converts the picture ordinarily seen by Nitze's instrument so that it occupies its correct position, though the illumination is somewhat enfeebled. The closer the cystoscope is to the bladder wall, the smaller the portion of mucous membrane seen, but the greater the magnification and *vice versa.*

In the female, H. A. Kelly's *open tubular cystoscope,* with distention of the bladder with air, is a satisfactory instrument.

For catheterization of the ureter, the *catheterizing cystoscope,* made by Wappler (New York) is a favorite instrument. For the sterilization of this cystoscope and of ureteral catheters formalin vapor is used.

(*b*) *Technic of Cystoscopy*

The patient lies on an examining table with the thighs spread apart and the urethra at about the level of the eyes of the examiner. The urethra is anesthetized with a 5 per cent solution of novocain. The urine is drawn off by sterile catheter, and the bladder filled with luke-warm boric acid solution (3 per cent), about 150 c.c. being passed in the male and 250 to 350 c.c., in the female. When the urine is turbid, the bladder must be thoroughly washed out before the examination is made.

The sterile cystoscope, lubricated with glycerin, is introduced and the current turned on to illuminate the bladder. The anterior wall of the bladder is syste-

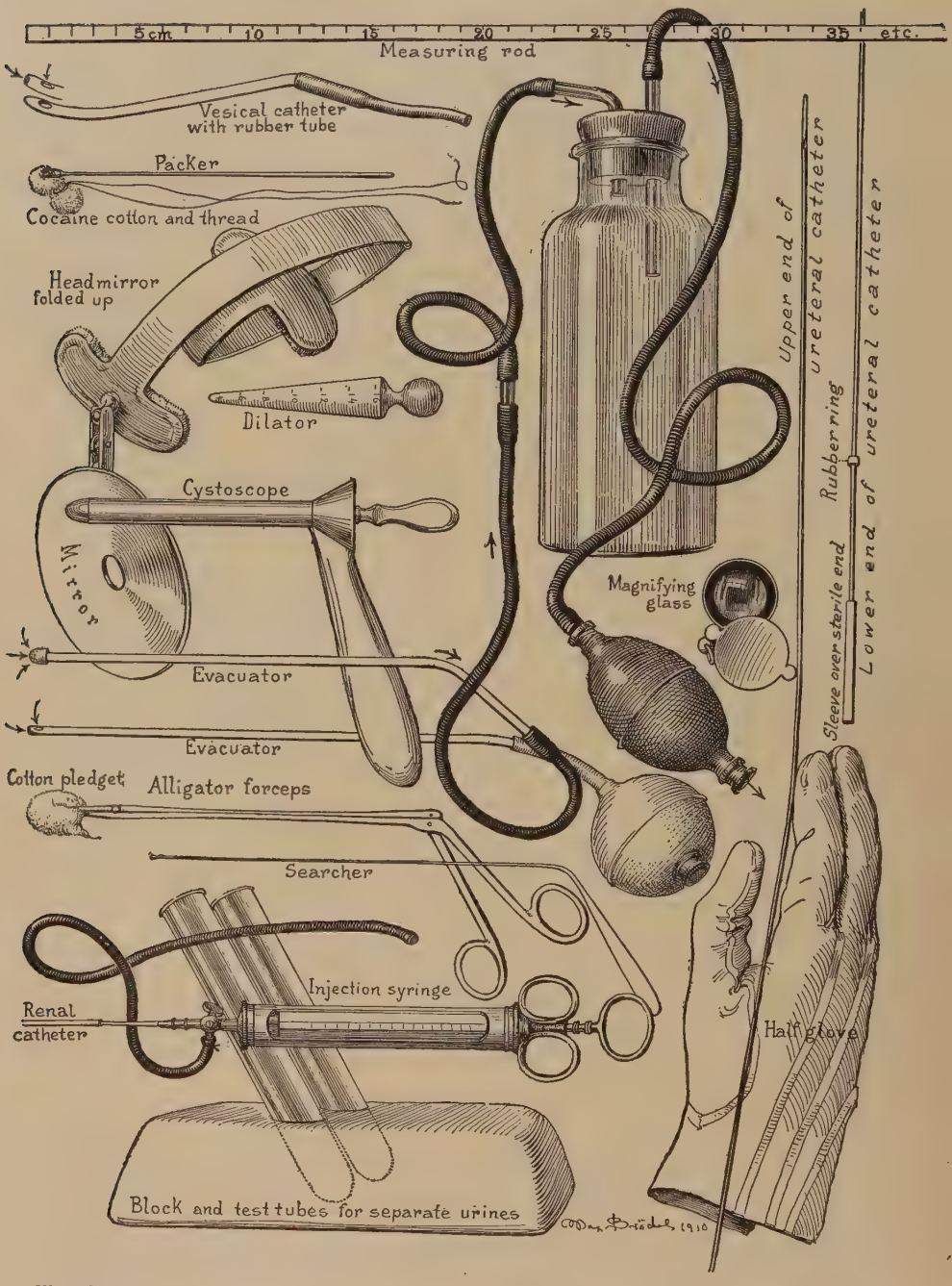

Fig. 464.—Chart Showing Instruments Used in Examination and Treatment of Bladder, Ureteral and Kidney Conditions in the Female. (After H. A. Kelly and C. F. Burnam.)

matically inspected by gentle rotation of the instrument on its long axis, and after each rotation shoving it backward and forward by raising and lowering it. The size and the distribution of the lobes of the prostate are observed and the results recorded on suitable forms.

(c) *Appearances on Cystoscopy*

Normally, the *mucous membrane of the bladder* is smooth, and of a yellow color. Here and there, a delicate bright red vessel may be visible.

Fig. 465.—Cystoscopic View of Right and Left Ureteral Orifices; Tuberculosis of the Left Kidney. Note Corona of Tubercles Around the Orifice of the Left Ureter, and the Normal Orifice on the Right. (After H. A. Kelly and C. F. Burnam.)

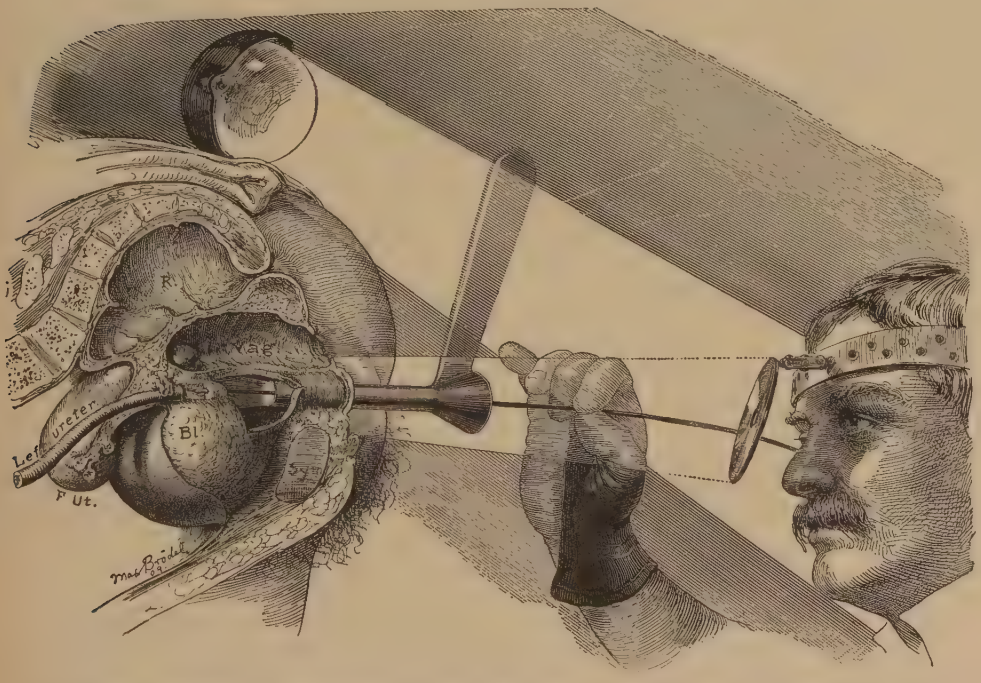

Fig. 466.—Beginning Catheterization of the Left Ureter in the Female in Knee-chest Posture through Open-air Cystoscope. Note Sterile Half-glove on Hand Holding Catheter. (After H. A. Kelly and C. F. Burnam.)

The *opening of the ureter* is usually found by watching for a sort of whirlpool occurring at intervals, due to the passage of urine from the ureter into the bladder. If any difficulty be experienced, a little indigo-carmin can be given by intramuscular injection, and in a short time (20 minutes) blue colored urine will appear at the ureteral opening.

This method of **chromocystoscopy** is used to some extent by surgeons for determining the relative function of the two kidneys. Thus, Völker and Joseph inject 4 c.c. of a warm 4 per cent solution of indigo-carmine into the gluteal

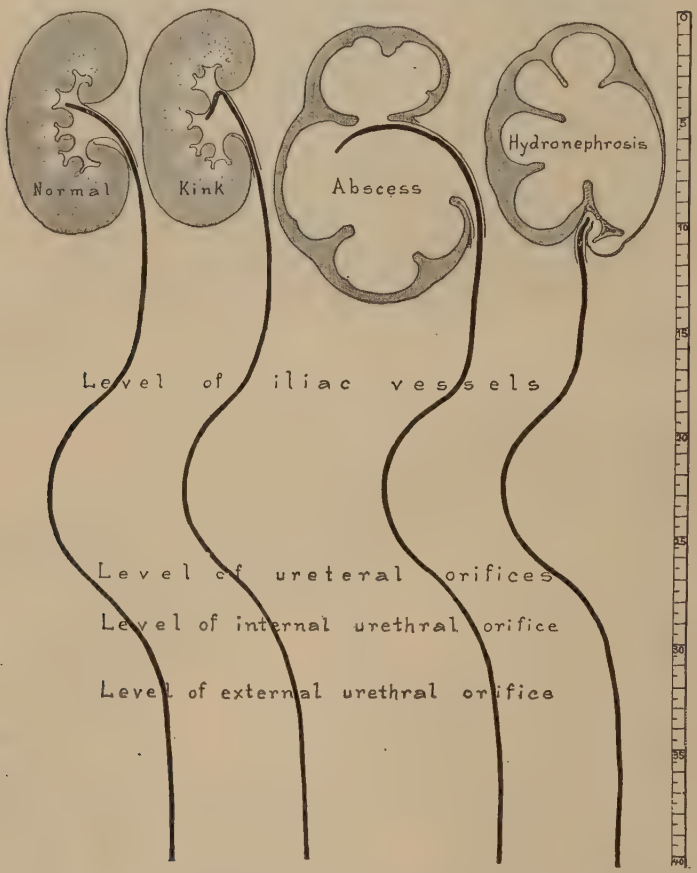

Fig. 467.—Various Shapes that a Soft Silk-rubber Catheter May Take in Its Course Up to the Kidney. A Catheter Allowed to Stay in Place a Few Minutes and Then Quickly Withdrawn and Put on a Cold Plate or in a Water-bath Will Assume the Same Shape It Had While in the Kidney. (After H. A. Kelly and C. F. Burnam.)

region, and then, through the cystoscope, observe the rhythm and the frequency of the urinary stream emerging from the ureter on each side. The urine assumes a blue color as early as twenty minutes after the injection. In unilateral renal disease, they saw (1) differences in the frequency of the jets of the stream and (2) differences in the color of the fluid emerging from the two ureteral orifices.

Instead of indigo-carmine, methylene blue may of course be used for the same purpose.

(*d*) *Ureteral Catheterization*

The appearance of *blood* or *pus* at one ureteral opening, while clear urine is seen to come from the other, points to unilateral disease; but usually a decision as to the state of the two kidneys is much more difficult than this and *ureteral catheterization*, with collection of urine from each kidney for examination, and the making of certain functional tests (*q. v.*), are necessary.

With the cystoscope in place, long, delicate, ureteral catheters can be passed, under the eye, through the ureteral orifices into the ureters, and,

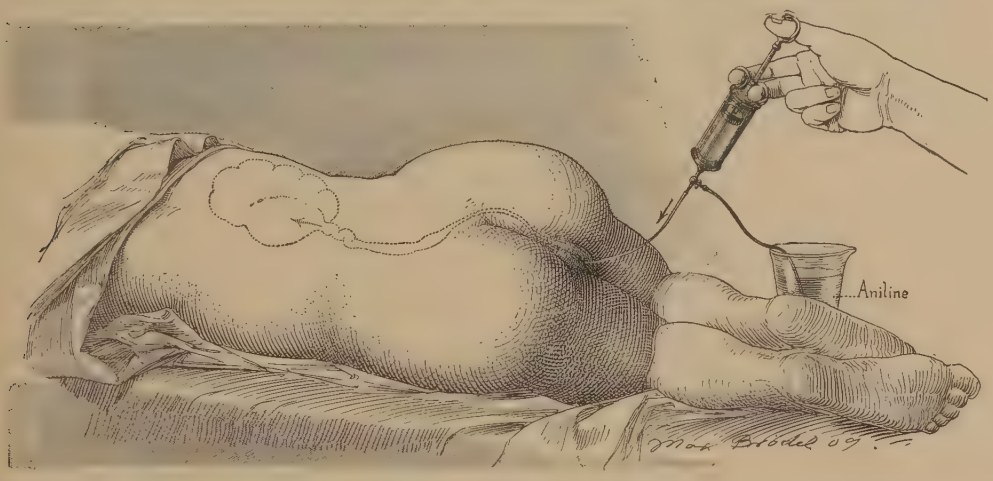

Fig. 468.—Illustration of Using Injection Method to Determine Capacity of Renal Pelvis in a Case of Hydronephrosis. Injection Should Be Carried on to the Point of Pain. (After H. A. Kelly and C. F. Burnam.)

when necessary, along them as far as the pelvis of the kidney. Once the ureteral catheters have been passed, the cystoscope can be removed and the catheters left in place for hours (labeled right and left).

Some cystoscopes permit the catheterization of both ureters at once; with others, only one ureter can be catheterized at a time.

It is often of help to inject a sterile fluid through the ureteral catheter for diagnostic purposes, for by this procedure we determine (1) the capacity of the renal pelvis, and (2) whether distention of the renal pelvis causes pain similar to that spontaneously felt by the patient.

Urine Segregators.—So-called *urinary separators*, or *segregators*, have also been used for collecting the urine from each kidney separately, in the bladder. The apparatus of Luys and Cathelin, or that of Harris, may be employed. They are, however, but little used though, occasionally, when ureteral catheterization is impossible, they may be helpful.

(e) *Pathological Findings on Cystoscopy and on Ureteral Catheterization*

On cystoscopy of the bladder, inflammatory changes may be visible (*cystitis*) in the form of hyperemia, hemorrhage, and deposits of fibrin or pus. In chronic cystitis, due to stricture, prostatic hypertrophy, etc., *trabeculation of the bladder* may be marked, with formation of *diverticula*. *Ulcers, stones* and *new growths* (polyps, cancer) become visible. In *tuberculosis,* there may be ulcers with small tubercles at their periphery.

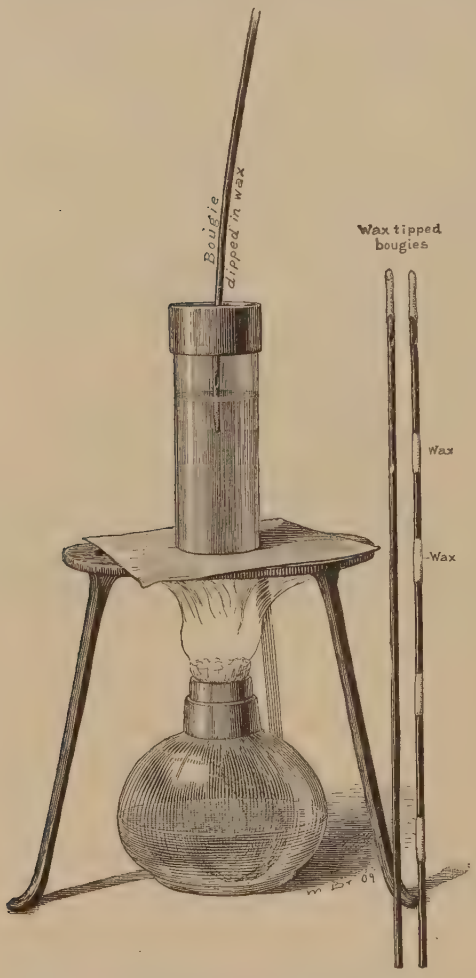

Fig. 469.—Waxing Tip of Renal Catheter. The Tip of the Catheter Is Dipped in Melted Wax, Which Hardens on Exposure to Air. The Proper Extent of Waxing the Tip Is Shown in the Catheter to the Right. In Certain Cases It Is of Advantage to Place Strips of Wax Along the Catheter, As Shown, or to Wax the Entire Catheter. (After H. A. Kelly and C. F. Burnam.)

The study of the *prostate* in disease has been greatly advanced by cystoscopic examinations (see Special Treatises).

Cystoscopy is especially important in distinguishing *hematuria* and *pyuria* of vesicle origin from renal hematuria and pyuria.

Ureteral catheterization permits of the diagnosis of unilateral diseases of a *ureter,* of the *pelvis of the kidney* or of the *kidney* itself (hemorrhages, inflammations, suppurations, strictures, stones, etc.). For the recognition of renal calculus, the passage of a *wax-tipped ureteral catheter* may be helpful. Sometimes, the spontaneous pains suffered by a patient can be exactly reproduced by *experimental distention of one renal pelvis* with fluid injected through a ureteral catheter. This method is often helpful in differential diagnosis. Unilateral functional renal diagnosis on ureteral catheterization has been previously described.

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4. Röntgenology of the Bladder and Ureters

Foreign bodies and stones in the bladder are often recognizable in x-ray plates. Stones consisting of urates, or of phosphates, may not be

Fig. 470.—Collargol in Three Diverticula of the Bladder After Draining Off the Collargol from the Bladder Itself. (X-ray Dept., J. H. H.)

visible as they throw only a slight shadow. For the diagnosis of such calculi, the passage of a sound, or a cystoscopic examination may be necessary.

The röntgenography is done with the patient in the recumbent position, with his legs extended, after his bladder and rectum have been thoroughly emptied, the plate lying beneath the sacrum, and the anticathode placed just above the symphysis pubis. It is best to use a tube diaphragm, directing it obliquely downward.

Burns in Young's clinic has found that if thorium be introduced into the bladder, the form can be beautifully demonstrated in röntgenograms, and a plate taken after emptying the bladder may reveal diverticula still containing thorium.

The ureters and the renal pelves are exquisitely demonstrable by röntgenography after injection of callargol, or better, of thorium, through the ureteral catheters.

Fig. 471.—Pyelography and Ureterography. Dilatation and kinking of the Ureter. Collargol Injection. (By courtesy of Dr. Baetjer and Dr. Waters, X-ray Dept., J. H. H.)

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G. Examination of the Male Genital Organs

In this domain, the urogenital specialists have worked out elaborate methods of examination. Only the technic of those most important for the general practitioner and the internist will be referred to here. For other methods, special treatises should be consulted.

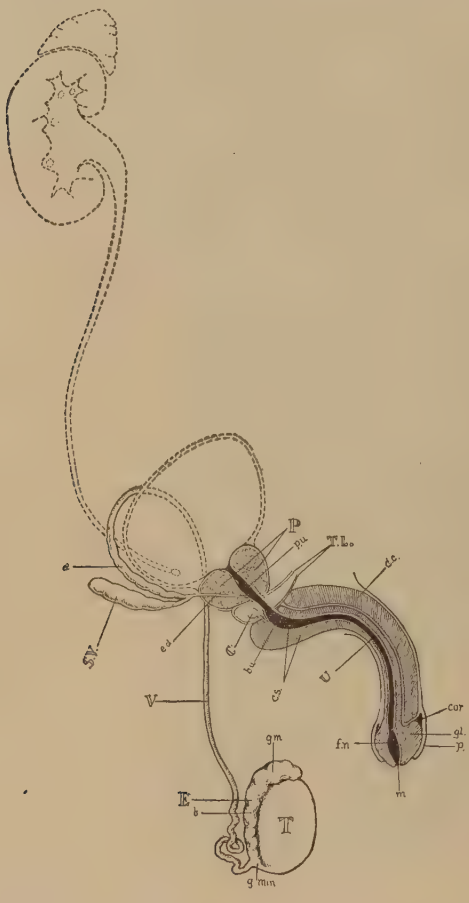

Fig. 472.—Lower Urinary Tract in the Male on Sagittal Section, and also the Internal and External Genital Organs. V, Vas deferens. S.V, Seminal vesicle. *a*, Ampulla. *e.d*, Ejaculatory Duct. E, Epididymis. *g.m*, Globus Major. *g.min*, Globus Minor. *b*, Body of the Epididymis. T, Testicle. P, Prostate. T.L, Triangular Ligament. C, Cowper's Gland. U, Urethra. *p.u*, Prostatic Urethra. *b.u*, Bulb of Urethra. *f.n*, Fossa navicularis. *c.c*, Corpus cavernosum. *cs*, Corpus spongiosum. *gl*, Glans Penis. *cor*, Corona. *p*, Prepuce. *m*, Meatus. (After R. Guiteras.)

1. Examination of the Male Urethra and Penis

(*a*) *Inspection of the Penis; Examination of Urethral Discharge*

On external inspection, we look for *malformations* (epispadias, or hypospadias), *para-urethral canals, narrowed external orifice* of the urethra, *redness* of meatus, *urethral discharge* (mucus, pus, blood), *scars* of old chancrous ulcers (soft chancre, hard chancre, herpes preputialis, carcinoma). At the same time we examine the *inguinal lymph glands* (buboes, metastases, etc.).

Any *urethral discharge* present should be subjected to microscopic examination. A drop is collected with a sterile platinum oese, spread on a glass slide, dried, fixed and stained with methylene blue, and a search made for *gonococci.* Gonococci occur in biscuit-shaped pairs usually inside of leukocytes. They decolorize by Gram's method and do not grow on ordinary media, though they can be grown on media containing human blood serum or ascitic fluid. (Plate XIX, Figs. 1 and 2.)

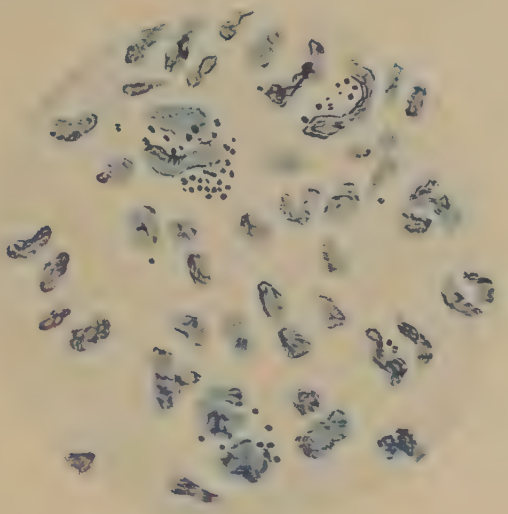

Fig. 1.—Gonococci, Methylene Blue. (After N. v. Jagic u. H. K. Barrenschen, "Atlas u. Grund. d. Klin. d. Mikroskopie," published by M. Perles, Wien.)

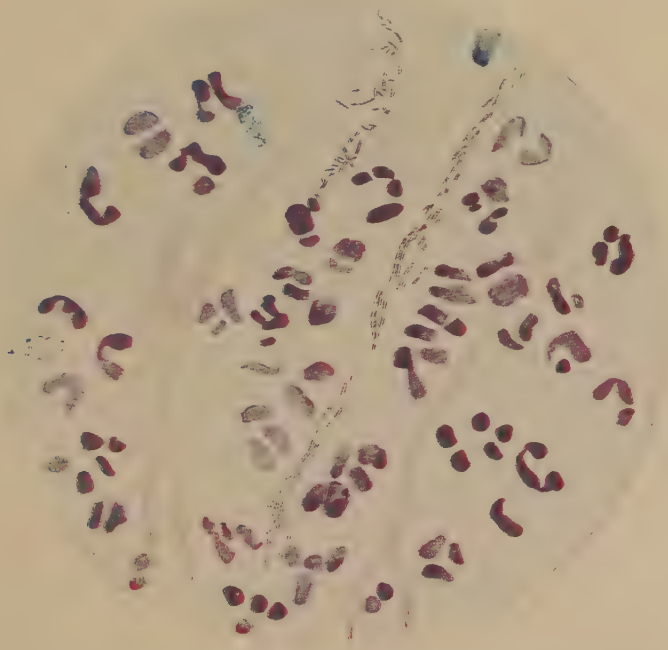

Fig. 2.—Streptobacillus of Ducrey in a Smear of Pus. (From Buschke, in E. Riecke's "Lehrb. d. Haut- u. Geschlechtskrankheiten," published by G. Fischer, Jena.)

If it be thought that a urethral discharge depends upon prostatorrhea, or spermatorrhea, a drop may be examined fresh. The presence of lecithin spirals indicates a prostatic origin, while spermatozoa, if present, will be visible. It should not be lost sight of that many neurasthenics suffer from a *urethrorrhea ex libidine*. It is a secretion from the glandulae urethrales [Littrei].

The occurrence of *priapism* may point to leukemia or to beginning tabes. A persistent *balanitis* may be an early symptom of diabetes mellitus.

A **soft chancre** (*ulcus molle*) is characterized by its multiplicity, its appearance in one to three days post coitum, its soft edges, and its frequent complication with *suppurating bubo* in the groin. In scrapings, the *bacillus of Ducrey* will be demonstrable.

A **hard or Hunterian chancre** (*ulcus durum*), the initial lesion of lues, is characterized by the fact that it is single and indurated, not only at its edges, but in the depth, that it is accompanied by *scleradenitis inguinalis*, that it does not appear usually until two or three weeks after the infecting coitus, and that it is later followed by symptoms of secondary lues (enlargement of the retrocervical lymph glands, skin exanthem). In scrapings, the *Treponema pallidum* can be demonstrated in dark field illumination or by the india ink method (see Part IV).

A simple **herpes preputialis** is sometimes mistaken for hard or soft chancre. Unlike hard chancre, it is usually very painful, especially when it first appears.

(*b*) *Endoscopy of the Urethra* (*Urethroscopy*)

Instrumental methods of examining the urethra by the urethroscope and by bougies and sounds belong to the special domain of surgical urology. Such instrumental examination is only occasionally necessary, even in genito-urinary disease, and should not be applied except when absolutely necessary for making a diagnosis or applying a treatment. Above all, one must avoid infecting the patient while making such examinations. If a urethroscope be used, it is best to choose an instrument, such as H. H. Young's, or Churchman's modification of it, in which the light is thrown in from without, rather than one in which the light is within the tube.

For the localization of catarrhal processes in the urethra and the diagnosis of certain obscure urethral lesions, urethroscopy is sometimes a real aid. It may also be employed for direct observation of a urethral ulcer, and for making a scraping for bacterio-diagnostic study (*Gonococcus; Bacillus of Ducrey; Bacillus tuberculosis; Treponema pallidum*). Or it may be useful in the treatment of persistent chronic local gonorrheal inflammations, and for making applications to the verumontanum.

(*c*) *The Two-Glass-Test and the Three-Glass-Test*

In the *two-glass-test* the patient is told to collect the urine in two separate parts, as nearly equal as possible, in clean receptacles, on rising

in the morning. If he be suffering from a catarrhal process of the anterior urethra (*acute* or *subacute anterior gonorrhea*), the first portion may be turbid while the second portion is clear; or he may have *both an anterior and a posterior urethritis*, in which case both portions may be turbid or contain shreds.

The reason for the use of the two-glass-test lies in the fact that, when the exudate is present only in the anterior urethra, it will be completely washed out by the first portion of urine voided, and the second portion will be clear. If there be an exudate coming from the posterior urethra, during the night, though some of it will remain in the posterior urethra itself, a part of it will go back into the bladder and be deposited in its lowest part, and, on voiding, the first portion of urine will be turbid, since it passes through the whole urethra, and the second portion will also be turbid, for, though the urethra has been washed clean, the exudate from the posterior urethra that has collected in the deepest part of the bladder will be passed.

Many urologists make use of a *three-glass-test*, and some even resort to a *five-glass-test*, but the latter is certainly superfluous.

I have found the *three-glass-test* very useful in differential diagnosis, especially in attempting to clear up the origin of albumin, pus, and blood in instances of albuminuria, pyuria, and hematuria, as one can often get clues for an origin of the material from the urethra, the prostate or the bladder.

Like the two-glass-test, it is best, when practicable, to make the three-glass-test when the patient rises in the morning. He is instructed to urinate successively into three glass receptacles, labeled I, II, and III. The urine in each should be examined as soon as possible afterwards. In *acute gonorrheal urethritis confined to the anterior urethra*, the urine in I will be turbid from pus, while II and III will be clear; but once the urethritis has become a *posterior urethritis* by extending backward into the pars prostatica (behind the M. sphincter urethrae membranaceae or "cut-off muscle" in the diaphragma urogenitale or triangular ligament) the discharge is bound to pass bladderward, mix with the urine in the bladder, and will then appear in receptacles II and III as well as in I.

In *hematuria*, the same rules hold; if the blood be derived from the anterior urethra, it will appear in I; if it come from the posterior urethra, II and III will also contain blood. Occasionally, blood will appear in III only, the bleeding occurring only at the end of urination, when it is squeezed out of the middle lobe of the prostate, or from the verumontanum.

Shreds in Glass III point to the prostatic ducts (chronic prostatitis). In *spermatorrhea*, spermatozoa are most abundant in III.

When a cystitis or a pyelitis is suspected to be due to *tuberculosis*, the centrifugalized sediment of III should be carefully examined for

Bacillus tuberculosis. One must make sure to rule out the *smegma bacillus.* To do this, the preputium, the glans penis, and especially the collum glandis should be thoroughly cleansed with soap and water and bichlorid solution and the pars cavernosa urethrae should be thoroughly irrigated with sterile water. The urine may be then passed into three sterile receptacles and the sediment in III examined for tubercle bacilli; if bacteria possessing the morphological and staining properties of Bacillus tuberculosis then be found, tuberculosis is certainly present, for the method used rules out the presence of extraneous bacteria like the smegma bacillus and other acid-fast bacilli (H. H. Young).

The "irrigation test" of Jadassohn may be employed instead of the three-glass-test if preferred. The patient is examined when his bladder is full. First, the anterior urethra is washed out with a warm solution of boric acid (3 per cent), by means of a Nélaton catheter placed in the external orifice of the urethra, the fluid being injected gently, or, better still, the irrigation can be made with a glass urethral nozzle. The patient may sit on the corner of a chair in order certainly to prevent the entrance of the fluid into the posterior urethra, or the perineum can be compressed during the washing. The anterior urethra is irrigated until the washings are perfectly clear. The patient then voids, and any turbidity due to urethral inflammation must come from its posterior part.

(*d*) *Palpation of the Urethra*

On external *palpation* of the male urethra, the walls of the tube can be felt throughout a large part of its extent. Inflammations, peri-urethral abscesses, foreign bodies in the urethra, or small urethral stones may be discovered. Inflammations of the bulbo-urethral gland of Cowper may cause a swelling, palpable on each side of the middle line between the anus and the scrotum. Intra-urethral chancres and long-standing tough strictures are sometimes palpable. One of the best ways to feel a stricture of wide caliber is to palpate along a sound in the urethra.

(*e*) *Röntgenography of the Urethra*

It is astounding what may sometimes be introduced into the urethra in perversions of the sexual sense. Foreign bodies of the most different sorts, including hair pins, nails, and clay pipe stems have been found in the urethra. These may usually be detected by palpation, by endoscopy, or by sounding; but in some cases a röntgenogram is illuminating. Small calculi from the kidney or from the bladder may lodge in the urethra and be visible in röntgenograms.

2. Examination of the Prostate

We study (1) the *external form*, and (2) the secretion from the prostate (*succus prostaticus*).

(*a*) *Palpation of the Prostate through the Rectum*

We gain a knowledge of the external form chiefly by rectal palpation, partly by catheterization, and by cystoscopy. The method of rectal palpation has been described in Part VIII. The prostate should be examined systematically per rectum. The patient should bend forward, resting his elbows on his knees. The index finger inserted into the rectum, explores systematically the *pars membranacea urethrae,* the *prostate,* the *vesiculae seminales,* and the *ductus deferens* on each side. The finger is first passed along the middle line between the two lobes of the prostate, and then the *right* and *left lobe* are separately palpated; it is important to establish the *upper* and the *lateral margin,* and the *size,* of each. One notes whether the *surface* of the prostate is smooth or rough, and the *consistence* (soft, medium, hard). One feels for *areas of increased resistance* (circumscribed inflammations or infiltrations), and asks the patient whether or not the palpation is painful. The reply is usually in the affirmative, and one then asks whether the sensation is only that of a *pressure* forward or whether *actual pain* exists. Pain is absent except in prostatitis (acute, subacute, chronic). The pain may be excruciating in prostatic abscess, when fluctuation may be made out.

Rectal examination does not inform us regarding the middle lobe of the prostate, or the part of the prostate directed toward the bladder; for this (1) the demonstration of a weakness of the bladder (residual urine), and (2) cystoscopic examination, are necessary.

In *benign enlargements* (prostatic hypertrophy), the prostate is usually smooth; in *malignant disease* (cancer) the surface is nodular. Prostatic *calculi* are sometimes palpable.

The size and thickness of the wall of each *seminal vesicle* and of each *ductus deferens* should be noted. These parts are often involved along with the prostate in chronic inflammations. Sometimes each vesicle feels larger and harder than normal, and the space between the two vesicles may be filled up by a broad, flat area of indurated tissue. When the periprostatic inflammation is extensive, the parts may become adherent to the pelvic wall on one or both sides. The seminal vesicles and the prostate may be *fixed* by such adhesions. Even when the prostate presents no abnormalities on palpation, it may contain an abnormal secretion (see below).

(*b*) *Examination of the Succus prostaticus*

To examine the prostatic secretion, it should be collected by the following procedure. The urethra and the bladder should first be thoroughly irrigated, without a catheter, with warm boric solution (3 per cent). The prostatic secretion is now expressed through systematic massage by means of the finger in the rectum. One begins at the upper margin of

each lateral lobe and presses downward toward the lower pole, gradually pressing every part of the gland. By this "stripping process," sometimes called "milking the prostate," a part of the secretion will enter the pars prostatica urethrae, whence a part of it may be further pressed forward by the finger, through the pars membranacea into the pars cavernosa, and pass forward and appear at the meatus, and a drop of it may be placed on a slide and directly examined microscopically. Another part of it will flow back through the posterior urethra into the bladder and mix with the little boric solution left there.

Fig. 473.—Digital Expression of the Prostate for Securing the Succus prostaticus for Examination. (After Luys, in O. Zuckerkandl's "Tech. d. Behandl. d. Harnorgane," in J. Schwalbe, "Ther. Tech.," published by G. Thieme, Leipzig.)

To the *naked eye,* the normal prostatic secretion is a grayish white fluid containing small particles. In disease, the fluid may be very turbid, yellowish and even purulent.

On *microscopic examination* of the fresh fluid, the prostatic origin of the fluid is made certain by the finding of *lecithin bodies* (round, non-nucleated, homogeneous fat-glistening structures, about the size of a red blood corpuscle or smaller). These are more significant than are *corpora amylacea* or the so-called *prostatic crystals* to be found in dried secretion. Normally, a few epithelial cells and an occasional leukocyte or red blood corpuscle may be present, but if many *pus cells* and *red blood corpuscles* are found, the condition is pathological.

The examination of a dried, fixed and stained smear (methylene blue) for *gonococci* is most important, since the long duration of chronic gonorrheal infections is very often dependent upon the harboring of gonococci in the prostate, or in the seminal vesicles.

3. Examination of the Seminal Vesicles

These may be palpated like the prostate, but they lie higher, diverging above the prostate on the two sides of the middle line. When inflamed, and especially when the site of abscess, the enlarged, painful sacs can be easily felt. Gonorrheal and tuberculous processes here are by no means uncommon.

The *contents* of the seminal vesicles can be expressed for examination if desired. It may be desirable to determine the presence or absence of spermatozoa.

4. Examination of the Testis, the Epididymis, and the Funiculus spermaticus

The *testis* is surrounded in its posterior circumference by the horseshoe-shaped *epididymis,* the head of the latter lying close to the upper extremity and its tail going over into the *ductus deferens,* close to the lower pole of the testis. The ductus deferens with its nerves and vessels and the tunicae make up the *funiculus spermaticus,* or spermatic cord, which passes through the inguinal canal and finally reaches the back of the bladder, to connect with the seminal vesicles, the prostate and the ejaculatory ducts.

On examining these structures, *palpation* is the principal method employed, though *inspection* is also helpful. One palpates the size and consistence of the testis and the different parts of the epididymis.

Enlargement of the testicle is met with in *orchitis* and in *gummatous tumor.* It is *small* in atrophy of congenital or inflammatory origin. Pressure on the testis normally gives rise to a sickening painful sensation. This *testicular sensation* on pressure may be absent in incipient tabes and in other organic nervous diseases.

In **enlargement of the epididymis,** its horseshoe-shape is usually retained (gonorrheal epididymitis, tuberculosis). Firm nodules in the epididymis are suggestive of tuberculosis, more rarely of lues.

In **hydrocele** of the tunica vaginalis propria the swelling may be large. It is usually unilateral and it is not connected with the inguinal canal (contrast with hernia). On palpation, it is felt as an elastic sac, which may fluctuate if tested in the longitudinal direction. The testicle and epididymis can usually not be felt. The percussion note is dull, in contrast with the tympany over hernia; and on transillumination (candle, electric light), the hydrocele is transparent. In **varicocele,** the dilated tortuous veins in the funiculus spermaticus feel like a bundle of worms.

5. Examinations for Sterility in the Male

In investigating the cause of a sterile marriage, the man should first be examined. In the *anamnesis,* we ascertain whether *impotence* or inability to perform the act of sexual intercourse exists (beginning tabes, neurasthenia, psychic impotence, etc.). In some cases, a history of *ejaculatio praecox* will be obtained; in others, external inspection will reveal a *hypospadias.* A history of *gonorrhea* is important, and *chronic gonorrhea* should be sought for. *Urethral stricture, chronic prostatitis,* or old *chronic epididymitis* may be responsible for sterility.

Of especial importance is the *examination of the sperm itself.* The patient is told to bring some of it. A drop should be transferred to a slide with a glass rod, since metal instruments may paralyze the motility of the spermatozoa. The slide and cover glass should be warm and the examination should be made on a warm stage, preferably in a hanging drop. Dried and stained specimens may also be examined for spermatozoa. In some cases, spermatozoa are entirely absent (*azoöspermia*).

Fig. 474.—Spermatozoa and Spermin Crystals —Testicular Cells and Leukocytes Are Also in the Field. (After P. Krause, "Lehrb. d. klin. Diagnostik d. inn. Krankh.," published by G. Fischer, Jena.)

Only after this anamnestic, physical and microscopical examination has excluded a cause of the sterility in the husband should the cause be sought in the wife. In some cases, no abnormalities can be found in either husband or wife, in which event the sterility may depend upon faulty relations between sperma and ovulum.

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H. Examination of the Female Genital Organs

We shall here consider (1) the ordinary gynecological examination, and (2) the special examination for the diagnosis of pregnancy.

Every practitioner should have practical training in gynecological examinations. I have always been grateful for the opportunities for practical work in gynecology and obstetrics that my first hospital interneship—a rotating service—afforded.

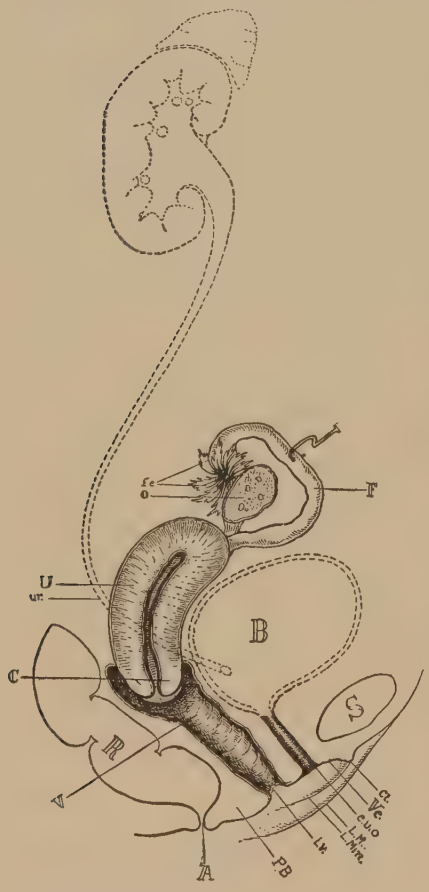

Fig. 475.—Genital Organs and Lower Urinary Tract in the Female on Sagittal Section. F, Fallopian Tube. f.e, Fimbriated Extremity. O, Ovary. U, Uterus. C, Cervix. B, Bladder. *ur*, Left ureter Passing Alongside Uterus. R, Rectum. A, Anus. S, Symphysis Pubis. *cl*, Clitoris. *Ve*, Vestibule. *e.u.o*, External Urethral Orifice. L.M, Labium Major. L.Min, Labium Minor. I.V, Introitus Vaginae. P.B, Perineal Body. (After R. Guiteras.)

1. The Ordinary Gynecological Examination

This consists principally of the so-called bimanual palpation with or without anesthesia; examinations with specula and sounds may occasionally be necessary.

(*a*) *Conditions of a Gynecological Examination and the Different Positions*

The patient should be completely undressed, except for a loose night-gown and stockings. All undue exposure is to be avoided. A trained nurse, a woman attendant, or a woman friend of the patient should be present. The examination may be made in any one of four positions, each of which possesses special advantages.

i. Gynecological Examination in the Dorsal Position

The patient lies on her back, at the end of an examining table, with her knees flexed, the thighs strongly drawn up on the abdomen, and the coccyx lifted so as to lessen the inclination of the pelvis. The thighs are supported by leg-holders or held by assistants.

ii. Gynecological Examination in the Knee-chest Position

The elbows and knees of the patient support the body. The shoulder-girdle

is in a low position, while the back and buttocks are high. The abdominal and pelvic viscera fall toward the diaphragm, and the attachments of the pelvic organs are stretched.

This position is especially valuable for examination of the bladder, the rectum, and the portio vaginalis uteri.

iii. Gynecological Examination in the Semiprone or Sims's Position

The patient lies on her left side with the left arm behind her, and allows the shoulder to sink as far forward as possible, the abdomen and chest resting upon the table. The knees are flexed, and the thighs drawn up.

This position is especially valuable for examination with the speculum, but it is not good for palpation of the lateral and posterior walls of the pelvis.

iv. Gynecological Examination with the Patient Standing

The patient stands with one foot on a low stool before the examiner. In this position the posterior and lateral walls of the pelvis can be thoroughly palpated.

The posture is especially valuable if the patient have a descensus or other displacement of the pelvic organs.

Examination under anesthesia may occasionally be necessary to relax the parts, though the greater the experience the less often will it be necessary to resort to it. When a vaginal examination is absolutely necessary in young unmarried women, anesthesia is desirable. In most cases, however, a rectal examination will suffice.

(*b*) *Special Points in the Anamnesis Preceding a Gynecological Examination*

The patient is asked when the *menses* first appeared, and whether they have been regular, how long they last, the amount of blood lost, the amount of pain experienced, etc. The number of *pregnancies* and *miscarriages* should be ascertained, with dates, and the course of the *puerperium*. The occurrence of discharges (*leukorrhea, menorrhagia*) and of *painful micturition* should be inquired into. *Pain* should be noted (character, location, severity), but it may be hard to value it for diagnosis.

(*c*) *Inspection of the Female Genitals*

The vulva, the urethral orifice, the vagina and the cervix are inspected (relaxed outlet, infection of Bartholin's glands, pus in the urethra, etc.).

The vagina can be inspected by means of Nelson's *trivalve speculum*. It is introduced by drawing back the posterior wall of the vagina with one or two fingers, then slipping in the lubricated instrument and pressing it a little backward, so as not to press upon the urethra or the pubic arch. The position of the cervix is ascertained by the finger, and the end of the speculum is directed downward and backward, so that, when opened, the cervix comes plainly into view between the three blades. If vaginitis, or endocervicitis exist, smears are made and stained for bacteria.

Examination by the speculum is *contra-indicated* in young unmarried women with slight genital affections, and in women suffering from severe inflammations or infections in the vestibulum. In very sensitive, nervous women, specular examination is best avoided.

(*d*) *Examination of the Bladder and of the Urine*

If the urethra be infected, the bladder should not be catheterized for diagnostic purposes. If the urethra be healthy, it is desirable to pass a sterile catheter after rendering the urethral orifice aseptic. By means of the catheter, the size, shape, position and sensitiveness of the bladder can be easily determined. If pathological conditions are found or suspected, cystoscopy and urethral catheterization may follow. Especial skill is required for such examinations.

(*e*) *Technic of the Bimanual Gynecological Examination*

Normal Position of the Cervix.—After the preliminary examination of the vagina and cervix, the exact position of the *portio vaginalis uteri* or *cervix* is ascertained. Normally, it lies behind the spinal line (connecting the spines of the ischiae), the external orifice of the uterus, or os, being directed backward, and the anterior lip being longer than the posterior. These three signs depend upon the *normal anteversion* of the uterus. The cervix should lie approximately in the median line.

Body of the Uterus.—Bimanually to palpate such an anteverted uterus, one places the fingers of one hand above the right pubic bone and presses gradually into the depth, while the fingers in the vagina shove the tissues just in front of the cervix strongly upward, the finger nail lying directly upon the anterior lip of the cervix. As soon as a resistance is felt by the external hand, the pressure of both hands may be slightly increased, when the *body of the uterus* can be felt between the two hands. Or the fingers in the vagina may press forward from the posterior wall, in which event the portio vaginalis, along with the body of the uterus, is shoved against the external hand. Should the uterus lie abnormally high, it may be necessary to press with the fingers directly against the tip of the cervix in order satisfactorily to palpate the uterine body.

To make sure whether a resistance felt is really due to the body of the uterus or not, a test is made to ascertain whether the portio vaginalis, which is certainly a part of the uterus, is connected or not connected with the resistance. In addition, we depend upon the *form* and *consistence of the uterus* as felt by the external hand. The *mobility of the uterus* (body and cervix) varies according to its size and weight, the condition of its ligaments, the tension of the abdominal walls, and the state of the adjacent organs. Normally, it should be easily possible, without pain, to press the uterus, with its fundus, upward as far as the upper margin of the symphysis pubis.

The *angle* between the cervix and the body, when the urinary bladder is empty, is obtuse in normal anteversion, and acute in anteflexion. The normal uterus is in a position of antedextroversion, the middle of the fundus gravitating slightly to the right.

Broad Ligaments and Parametrium.—On pressing firmly with the two hands near the lateral margins of the uterus, the broad ligament (*ligamentum latum uteri*), on each side, may be examined, and abnormal conditions of the *parametrium* will be found, if present, in the transverse pelvic diameter, to the right and to the left of the uterus.

The pouch of Douglas (*excavatio recto-uterina*) behind the uterus and the peritoneal pocket between the uterus and the bladder (*excavatio vesico-uterina*) cannot be demonstrated normally on palpation, but if they be filled with blood, ascitic fluid, or inflammatory exudate, the projecting lower part of the pocket can be felt. The recto-uterine muscle (*M. recto-uterinus*), running in the lateral folds (*plicae recto-uterinae*) bounding Douglas's pouch, can be palpated from the vagina but still more easily from the rectum, and the latter examination should always be made in affections of the *pelvic peritoneum* or parametric tissue. A round ligament (*Lig. teres uteri*) cannot be felt when the uterus is normal, though it may be palpable when the uterus is enlarged, as in pregnancy.

Uterine Adnexae.—The palpation of the *uterine adnexae* (fallopian tubes and ovaries) is a most important part of the examination. One feels them by palpating in the oblique diameter of the pelvis lateral from, and behind, the uterine body. Of the fallopian tube (*tuba uterina*), the *isthmus* is normally palpable and, sometimes, also the *ampulla*. *Dilated* and *thickened tubes* are easily palpable. They are distinguishable from other tissues by their elongated shape, which they retain even when markedly enlarged (fishworm-form, retort-form, sausage-form, etc.).

The *ovaries* are far more mobile than the fallopian tubes and are, accordingly, much more frequently found in an unusual position. In the adult, each ovary has the form of a flattened ellipsoid, its lateral surface lying directly in contact with a depressed portion of the peritoneum of the lateral wall of the pelvis below the pelvic inlet. The medial free surface is, normally, directed toward the rectum. To reach it on bimanual palpation, one searches in the oblique diameter of the pelvis, shoving the intravaginal or the intrarectal finger as far forward behind the cervix through the posterior fornix of the vagina as possible, while the outer hand makes rolling movements on the abdominal wall, passing medialward from the wall of the pelvis toward the uterus.

The *ovary* is recognized by (1) its position, (2) its flattened, bean-shape, (3) its movability, (4) its elasticity, and (5) its normal characteristic tenderness. It is rare that the two ovaries lie exactly symmetrically.

In infantilism, an *undescended ovary* is common. In many adults, *prolapse of the ovary* is found, the organ on one or both sides hanging down into Douglas's pouch, where it may be either loose or fixed.

Other Structures.—On making a vaginal examination, attention should always be paid also to the condition of the rectum, the sigmoid, the cecum, the vermiform appendix and the urinary bladder and ureters, as important data regarding these structures can often thus be obtained.

Abnormal Findings.—The details of the findings in pathological conditions cannot be gone into here; for them, special text-books of gynecology should be consulted. But every practitioner should make it a rule, when female patients complain of symptoms that point directly or indirectly to the genital apparatus, or where vague symptoms cannot be accounted for by disease outside the pelvis, either to make a thorough gynecological investigation himself, or to have a gynecologist do so. Certain exceptions should, perhaps, be emphasized. In hysterical women, and in the insane, gynecological examinations are to be avoided unless conditions make them imperative.

Gynecological examinations should, of course, not be made while a patient is menstruating, except in special cases where it may be desirable to make use of the normal dilatation of the internal os, which accompanies menstruation, for examining the interior of the uterus (e. g., for submucous uterine myoma).

(*f*) *Examination with the Uterine Sound*

Since the development of the technic of bimanual examination, the uterine sound need be but little used, though it may occasionally be necessary in connection with intra-uterine disease (endometritis, carcinoma), or in stricture of the vagina or neck of the uterus (dysmenorrhea, sterility, etc.).

Above all, *the sound should never be passed for diagnostic purposes if there be any suspicion of the existence of pregnancy*, unless abortion has already begun (hemorrhage, discharge), and then only when it is possible immediately afterward to empty the uterus if necessary. Nor should a sound be passed when there is evidence of acute purulent infection of the vagina or cervix. The history of gynecology has many lamentable examples of *infection* and of *perforation of the uterus* from the passage of a sound.

Technic.—The strictest *asepsis* and the *most delicate manipulation* should be observed on the passing of a uterine sound. The sound is grasped by its handle and held like a pen; it is guided to the cervix along the index finger of one hand into the cervical canal, the tip of the sound being directed upward at first. An obstruction will be met near the internal os, but if the tip of the sound be allowed to rest there for a few moments it usually lets up, especially if the handle be slowly and gently depressed toward the perineum (anteflexion), or, in the case

of retroposition, by turning the sound through 80° and moving the handle gently toward the symphysis.

When the tip of the sound touches the wall of the fundus, another slighter resistance will be felt, when the forward movement is to be terminated abruptly. If the uterine wall be soft, perforation can easily occur. *Caution!*

Abnormalities.—By means of the sound, any *abnormal contents* of the uterus may be explored; foreign bodies, products of inflammation, tumors, or imperfect abortions may thus be detected. A systematic examination of the intra-uterine wall may be necessary.

(*g*) *Diagnostic Dilatation and Curettement*

In rare cases, where serious clinical phenomena inexplicable otherwise make it necessary, *dilatation of the cervix for digital examination of the interior of the uterus* may be required. The method of dilating slowly by tents should never be used (danger of infection). *Gradual dilatation* by Hegar's dilators is sometimes used; but *rapid dilatation* is the safest, and is most generally employed (Goodell-Ellinger dilators). After dilatation, *curettage* can be done if necessary, and the microscopic examination of "uterine scrapings" thus obtained may be very important for diagnosis (polyp, carcinoma, endometritis, retained placenta, etc.).

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2. Special Examination for the Diagnosis of Pregnancy

This is one of the most frequent and important examinations in connection with the female genital organs that the practitioner is called upon to make, and every physician should be capable of undertaking it. In the majority of cases, a decision is easy, though in a few cases, the most skilled may be deceived.

(*a*) *Inspection of the Abdomen, the Back and the Breasts*

This should be made first in the recumbent position. Any changes in the *appearance of the abdomen and back* can thus be observed. In advanced pregnancy, there is an exaggeration of the lordosis of the lumbar spine and of the kyphosis of the sacrum from the weight of the pregnant uterus and the necessity of restoring equilibrium. The abdomen projects upward and forward, the main expansion being in the median and right lateral parts from the symphysis toward the right costal margin, in contrast with other bulgings of the abdomen (ascites, tympanites, obesity, tumors). The *lineae albicantes* are not specific for pregnancy but may follow stretching of the skin from any cause. The tendency to *pigmentation* in the linea alba, about the umbilicus, and around the nipples is common. In brunettes this is of a dark brown or a black color; in blonds, it is of a reddish brown color.

The *breasts* show signs from the second month on (increase of the gland substance and of fat; colostrum can be expressed; pigmentation; and, especially, the slight prominence due to hyperthrophy of Montgomery's glands).

(*b*) *External Palpation of the Uterus and Its Contents*

External examination will not permit of a decision regarding the existence of pregnancy before the fourth month, as the fundus of the uterus does not become palpable from the outside earlier. When pregnancy is sufficiently advanced, a feeling of *contraction of the uterine wall* on palpation is of great help in diagnosis.

In the second half of pregnancy, the palpation of parts of the fetus itself and the auscultation of the fetal heart sounds are important diagnostic criteria.

One palpates with warm, dry hands, systematically, and seeks, first, for the *fetal head.* Standing with his back toward the head of the patient, the physician places both hands flat on the abdomen, the little finger lying along Poupart's ligament on each side. Gently and slowly pressing into the depth, the two hands are made to approach one another. Should the fingers of one hand feel some part of the fetus, the movement of that hand is arrested, while the other hand continues the palpation until it reaches the same part. The fetal head is recognized by its size, roundness, hardness, and its ballottement. If the position of the head be made out, it is next desirable to determine the position of the *back* and the *extremities.*

(*c*) *Auscultation of the Heart Sounds of the Fetus and Electrocardiography of the Fetal Heart*

The auscultation of the fetal heart sounds yields the most certain proof of the existence of pregnancy and of a living fetus. It also helps in the diagnosis of the position of the fetus, and of the existence of a twin pregnancy.

The stethoscope is placed on the skin, the patient changing her position several times, if the fetal heart sounds be not readily found. The mother's pulse is palpated simultaneously with the auscultation in order that a uterine souffle be not taken to be a fetal heart sound.

The fetal heart sound may not be audible, even when the child is alive if the back of the fetus be directed backward. The fetal heart *rate* varies between 120 and 160 a minute. It is asserted that *girls* have a faster rate than *boys* (139 : 136). The sounds are most often heard in one lower quadrant of the abdomen.

With electro-cardiography the *electro-cardiagrams of the maternal and the fetal heart* can be graphically recorded on a single film; the fetal EK is easily distinguishable from the maternal EK.

(*d*) *Combined Internal and External Examination*

If it be desired to establish the diagnosis of pregnancy before the third or fourth month, combined internal and external (bimanual) examination must be made. The greatest care should be used to avoid any possibility of infection, and internal examination should preferably be made with the aid of a sterile rubber glove.

The examination may be preceded by *inspection of the external genitals.* The *lividity* of the genital mucous membrane, its *turgor,* and the *pigmentation* of the external genitals belong to the uncertain signs of pregnancy. Internally, the *softness* of the vaginal mucous membrane and of the cervix are striking. The rough rule has been laid down that

the cervix of the non-pregnant uterus feels like the chin, whereas a softness corresponding to the tip of the nose points strongly to pregnancy.

The *compressibility* of the wall of the uterus between the external hand and the internal finger, either (1) of the supravaginal portion of the cervix, the vaginal finger in front of the uterus and the external hand pressed deep down *behind* the uterus, or (2) as a fold on the anterior wall of the body of the uterus, the vaginal finger in front of the uterus, the external hand pressed down between the uterus and the bladder; these two signs known as Hegar's signs of pregnancy, may be met with as early as from the 4th to the 8th week. Later on, portions of the fetus can be felt (especially by ballottement) in the lower uterine segment on bimanual examination.

The diagnosis of pregnancy can nearly always be made by the 6th week.

(*e*) *Abderhalden's Test for Pregnancy*

With the aid of Abderhalden's ninhydrin reaction, a specific ferment for the disintegration of placental tissue can be demonstrated very early in pregnancy in a large majority of the cases examined. The principle of this test has been discussed in Part VII (*q. v.*).

The technic is too delicate to permit of the use of the method by the general practitioner. But the blood can be carefully drawn and sent to a special laboratory for examination, or, better still, the patient may be referred to the laboratory worker directly for withdrawal of the blood with observance of special precautions essential for the proper performance of this test.

(*f*) *Examination for Extra-uterine Pregnancy*

The necessity of making a diagnosis of an *extra-uterine pregnancy,* and especially of a *ruptured tubal pregnancy* or a *tubal abortion* may fall to the lot of any practitioner any day. The anamnesis is very helpful. If one or two menstrual periods have been missed, and then irregular uterine hemorrhage has set in, and then an attack of severe pain with vomiting and collapse has been suffered, and a swelling be palpable in one lower quadrant of the abdomen, there will be but little doubt of the diagnosis. It is sometimes, however, difficult to differentiate the peritubal hematoma of ruptured tubal pregnancy (1) from *appendicitis,* (2) from a *unilateral pyosalpinx* with perisalpingitis, or (3) from a *normal pregnancy complicated by appendicitis.* But in all these conditions, an exploratory laparatomy is indicated. The important thing is to recognize the necessity of immediate operation and to see to it that there is no delay.

(*g*) *Röntgenology of Pregnancy*

Recently, a number of papers have appeared bearing upon röntgenological examinations of the pregnant uterus. For the details of the technic and the precautions to be observed, the original papers should be consulted.

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Part X

SECTION II

SPECIAL DIAGNOSIS OF THE DISEASES OF THE UROGENITAL APPARATUS

In this section we shall consider the special diagnosis of:

A. The diseases of the kidneys;
B. The diseases of the urinary passages (ureters, urinary bladder);
C. The more important diseases of the male genital organs; and
D. The more important diseases of the female genital organs.

A. Special Diagnosis of Diseases of the Kidneys (The Nephropathies)

1. Classifications of the Nephropathies

(*a*) *Unsatisfactory State of the Subject*

In no part of medicine, perhaps, unless it be with the arthropathies, does so much confusion exist with regard to terminology as with the renal diseases or nephropathies. It is easy to understand why. Classifications are needed, and used, for different purposes. A classification suited to the needs of the pathological anatomist will not suffice for the needs of the pathological physiologist. Or, again, classifications set up by the etiologist are often hard to harmonize with classifications based upon clinical symptoms, upon pathological-physiological phenomena, or upon post mortem findings regarding structure. Clinical men have often tried, in their clinical classifications, to value all kinds of studies—clinical, etiological, pathological-physiological, and pathological-histological. This is desirable and laudable, but knowledge is not yet sufficiently advanced to permit us to make etiological, anatomical, and clinical classifications fully coincide. Every clinical classification must, at present, be in the nature of a compromise. We must needs make the best of the difficult situation in which we find ourselves.

(*b*) *Commoner Clinical Forms of Nephropathy*

Clinically, the *commoner forms* of nephropathy (leaving out passive congestion and pyelitis) are divisible into three great groups:

I. *Cases of acute renal disease (or nephropathy), with, or without, edema.*

Here are included acute tubular degenerations (or the nephroses) and acute glomerulonephritis (diffuse and focal).

II. *Cases of subacute or subchronic renal disease (or nephropathy), with "renal" edema occurring in their course.*

Here are included the subacute and subchronic glomerulotubular nephropathies which give rise to the "large white" and the "large variegated kidney."

III. *Cases of chronic renal disease (or nephropathy), without "renal" edema, lasting perhaps for years, and terminating, ultimately, by apoplexy, cardiac failure, or uremia.*

Here are included the (1) "primary contracted kidney" (or "diffuse arteriolar nephropathy"), (2) the "secondary contracted kidney" (the end stage of some cases of chronic glomerulonephritis), and (3) the focal form of atherosclerotic nephropathy, in which the kidney need not undergo general contraction.

(*c*) *Attempt to Classify the Nephropathies on an Etiological-Pathological Basis*

From the *etiological-pathological standpoint*, I have attempted to classify the commoner forms of renal disease as follows:

I. Renal Diseases Due to Injuries Reaching the Kidneys through the Blood (Hematogenous, or Descending Nephropathies).

A. Diffuse hematogenous nephropathies due to soluble toxic substances.

(*a*) Tubular degenerative nephropathies or so-called nephroses (e. g., sublimate kidney, phosphorus kidney, bichromate kidney, pregnancy kidney, hemoglobinuric kidney, kidney of cholera, yellow fever and other acute infections).

(*b*) Glomerulonephritis (acute, subacute, chronic), due most often to streptococcus toxins.

(1) Catarrhal form with desquamation and proliferation of capsular epithelium.

(2) Intracapillary or thrombosing form of glomerulitis.

TABLE GIVING THE URINARY FINDINGS IN THE MORE COMMON DISEASES OF THE KIDNEYS AND URINARY PASSAGES

Form of Disease	Amount of Urine	Color	Specific Gravity	Amount of Albumin	Sediment	Duration	Results, Accompaniments, etc.
Stasis kidney.	Scanty.	Dark.	High.	Slight or moderate.	Urates; occasional casts and red blood cells.	As long as stasis lasts.	Cardiac death; infarctions.
Acute nephropathy.	Oliguria or anuria; rarely polyuria.	Dark, occasionally bloody.	High to normal.	Usually large.	Abundant; red blood cells; white blood cells; granular, hyaline, blood and epithelial casts.	Weeks to months.	Uremia common; sometimes arterial hypertension; edema common.
Chronic nephropathy with renal edema (chronic parenchymatous nephritis; chronic glomerulotubular nephritis).	Oliguria.	Dark.	High.	Large.	Abundant; all varieties of casts; fatty epithelium; red blood cells.	Death, a few months to one or two years; rarely healing with secondary contraction of kidney.	General anasarca. Heart hypertrophy. Usually increased blood pressure. Uremia common.
Chronic nephropathy without renal edema (contracted kidneys, most often diffuse arteriolar nephropathy).	Polyuria.	Pale.	Low, usually.	Trace.	Very little; occasional cast or red blood cell.	Years; decades.	Progressive arterial hypertension to 220 or 260 or more; cardiac hypertrophy; no dropsy until myocardial insufficiency sets in. Death from apoplexy, uremia, cardiac failure, or, often, terminal infections.
Amyloid kidneys.	Normal or polyuria.	Pale.	Normal or low.	Variable; often much.	Slight; hyaline, granular, and waxy casts.	Months to years.	Marked edema usually; no uremia; normal or subnormal blood pressure; no heart hypertrophy; chronic suppuration, tuberculosis or lues as etiology.
Pyelitis.	Normal or polyuria.	Turbid.	Normal or low.	Slight.	Pus cells; pelvic epithelium (casts only when complicated by pyelonephritis or other nephropathy).	Acute or chronic.	Fever; pain; etiology may be evident.
Cystitis.	Normal or oliguria.	Turbid, sometimes bloody.	Normal.	Slight, due to pus.	Slight; pus cells; red blood cells; squamous epithelium; triple phosphates.	Acute or chronic.	Alkaline urine; ammoniacal odor; complicated often by pyelitis and pyelonephritis.

(*c*) Diffuse arteriolar nephropathy (chronic), probably due to action of toxic substances on the organ arterioles in various parts of the body, and causing atherosclerosis in the kidney of the vasa afferentia of the glomeruli with resulting atrophy of renal units.

(*d*) More focal atherosclerotic nephropathy, in which though the action of the causal toxic substances is diffuse, certain only of the renal vessels undergo change, probably owing to local disposition and a "patchy atrophy" develops.

B. Focal hematogenous nephropathies due to bacteriemias.

(*a*) Embolic (purulent) nephritis from streptococcus and staphylococcus.

(*b*) Embolic hemorrhagic (non-purulent) glomerulonephritis (large red or variegated kidney due to streptococcus viridans).

(*c*) Acute interstitial nephritis, non-suppurative, with lymphocytic exudate after scarlet fever.

(*d*) Excretory bacterial nephritis (*nephritis papillaris mycotica* of Orth) (casts of cocci).

II. Renal Diseases Due to Injuries Reaching the Kidneys through the Urine (Urinogenous, or Ascending, Nephropathies).

(*a*) Hydronephrotic nephropathy (due to obstruction in urinary passages) depending on renal calculus, ureteral obstruction, prostatic hypertrophy, stricture of urethra, etc.; it may be unilateral or bilateral.

(*b*) Pyelonephritis.

(1) Pyogenic.

(2) Tuberculous.

Recently, Volhard and Fahr, in their excellent monograph on Bright's Disease, have attempted a similar classification as follows:

A. Nephrosis.

I. Simple Nephrosis:

(1) Stage of cloudy swelling (= pure parenchymatous change).

(2) Stage of histologically demonstrable degenerative changes in renal epithelium.

(3) Stage of inflammatory reaction in connective tissue.

(4) Scar stage.

II. Special Nephrosis.

(1) Poisons.

(a) Sublimate.

(b) Chromate.

(2) Amyloid kidney.
  (a) Degeneration.
  (b) Inflammation.
  (c) Scarring.

B. Nephritis.

I. Diffuse Glomerulonephritis:
  (1) Acute.
  (2) Subacute or subchronic (= large white kidney).
  (3) Chronic glomerulonephritis (= Secondary contracted kidney).

II. Focal Nephritis:
  (1) Focal glomerulonephritis.
  (2) Acute Interstitial, non-suppurative, nephritis.
  (3) Embolic focal nephritis.

C. Arteriosclerotic Kidney.

I. Pure arteriosclerotic kidney.

II. Combination forms.

They have also set up rules of differential diagnosis by means of which they believe that, in the majority of cases, at any rate, the form of pathological lesion that exists can be recognized during life.

Differential Diagnostic Schema of Volhard and Fahr

Clinical Symptom of:	Appears to be Dependent upon:	Occurs:	Is Differentiated by the symptom:	The Differentiating Symptom is:
Edema.	Epithelial degeneration.	In pure degenerative (nephrosis).	Increase of blood pressure.	Absent or rare.
		In true inflammation.		Present.
Hematuria.	Inflammation.	In focal nephritis.	Increase of blood pressure.	Absent.
		In diffuse nephritis.		Present.
Moderate increase of blood pressure and slight cardiac hypertrophy.	Diffuse involvement of the renal vessels.	In chronic diffuse, glomerulonephritis.	Inability of kidney to concentrate.	Absent.
		In terminal stage of the same—secondary contracted kidney.		Present.
Inability of the kidney to concentrate.	Absence of a great part of the secretory elements.	In the end stage of nephrosis.	Increase of blood pressure and cardiac hypertrophy.	Absent.
		In the end stage of nephritis.		Present to a moderate degree.
		In the end stage of combination form.		Present in a high degree.
Excessively high blood pressure and marked cardiac hypertrophy.	Diffuse arteriosclerosis of the renal vessels.	In the benign hypertonic conditions.	Disturbance of the renal function up to complete inability to concentrate.	Absent.
		In the malignant combination form. Sclerosis plus nephritis.		Present in varying degrees.
		In the secondary contracted kidney, plus sclerosis of the renal vessels.		Present in an extreme degree.

In the article on renal diseases in Osler and McCrae's *Modern Medicine,* J. B. Herrick, in a carefully written article on Nephritis, adopts Senator's classification of the chronic forms, as follows:

1. Chronic parenchymatous nephritis (Chronic diffuse nephritis without induration).
2. Chronic interstitial nephritis (Chronic diffuse nephritis with induration).
   (a) Primary chronic interstitial nephritis.
   (b) Secondary chronic interstitial nephritis.
   (c) Arteriosclerotic kidney.
3. Mixed type, a combination of (1) and (2), *i. e.,* diffuse nephritis.

In Osler's Principles and Practice of Medicine (1912), under the term *Acute Bright's Disease,* are included practically all the acute forms of nephropathy (toxic and inflammatory) while under *Chronic Bright's Disease* are included (1) chronic parenchymatous nephritis and (2) chronic interstitial nephritis (both the primary and the secondary contracted kidney).

Important contributions to the classification of renal diseases have been made by American pathological anatomists, notably by Councilman, Mallory, Ophüls, Oertel, and Winternitz.

For the purposes of systematic description in the present volume, I shall consider the various forms of renal disease under the following headings:

I. The Congenital Nephropathies;
II. The Nephropathies of Circulatory Origin;
III. The Toxic Degenerative Nephropathies, or the Nephroses;
IV. The True Inflammatory Nephropathies, or the Nephritides;
V. The Nephropathies associated with Diseases of the Renal Pelvis;
VI. The Parasitic Nephropathies; and
VII. The Neoplastic Nephropathies.

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2. The Congenital Nephropathies

These include the malformations of the kidney. The classification of these given by Newman is convenient, and is as follows:

A. Displacements of the kidney without mobility.

1. Congenital displacement without deformity.
2. Congenital displacement with deformity.
3. Acquired displacements.

B. Malformations of the kidney.

1. Variations in *number,* including (*a*) supernumerary kidney; (*b*) single kidney, due either to congenital absence of one kidney or atrophy of one organ; and (*c*) absence of both kidneys.
2. Variations in *form* and *size,* including (*a*) general variations in form, lobulation, etc.; (*b*) hypertrophy of one kidney; and (*c*) fusion of two kidneys, as in the horseshoe kidney, the sigmoid kidney and the disk kidney.
3. Variations in the *renal pelvis,* the *ureters* and the *renal blood vessels.*

The two most important conditions to be considered clinically under this heading are (1) *Movable Kidneys,* and (2) *Congenital Cystic Kidneys.*

(*a*) *Movable Kidneys*

(Ren Mobilis, Wandering Kidney, Floating Kidney, Nephroptosis)

Definition.—An abnormal mobility of one or both kidneys.

Etiology.—The condition is often due to congenital relaxation of the peritoneal attachments, sometimes to the existence of a mesonephron, or it may be a part of a general visceroptosis. In many instances, the condition is acquired, owing to the effects of tight-lacing, or repeated pregnancies. The condition is much more common in *women* than in men, the proportion being 7:1. The *right* kidney is much more often mobile than the left (7:1); in some instances, both kidneys are abnormally mobile.

Marked loss of weight is a common precipitating cause. The best support to the kidney is a well-developed fat layer about it.

Symptoms.—There may be no symptoms whatever, or at most, a sense of weight or dragging, a little pain in the back, or intercostal neuralgia. In thin, nervous people it is often associated with dyspeptic and neurasthenic symptoms, but it need not be the cause of these. Adjacent structures are sometimes compressed by a mobile kidney (duodenum, bile ducts, intestine).

In some patients, usually women, remarkable attacks, known as Dietl's crises recur from time to time in the right side. Each attack consists of a sudden colicky pain, often very severe, radiating into the back and along the ureter. Along with the pain there is usually a chill, nausea, often vomiting, fever and collapse. There is oliguria and sometimes hematuria. In the region of the right kidney there is tenderness on pressure. In some cases there is no local swelling; in others there is a palpable mass, due to dilatation of the pelvis of the kidney (intermittent hydronephrosis). Dietl's crises are supposed to be due usually to a kink of the ureter or of the renal vessels. After an attack is over there may be a sudden polyuria, with disappearance of the local swelling.

Several degrees of mobility of the kidney have been described (see Fig. 476). If only the lower pole of the kidney can be felt on deep inspiration, it is a *palpable kidney;* if the kidney can be "captured" (see Examination of the Kidney) and held down, though not below the level of the umbilicus, it is a *movable* kidney; if the organ is still more mobile, so that it may be

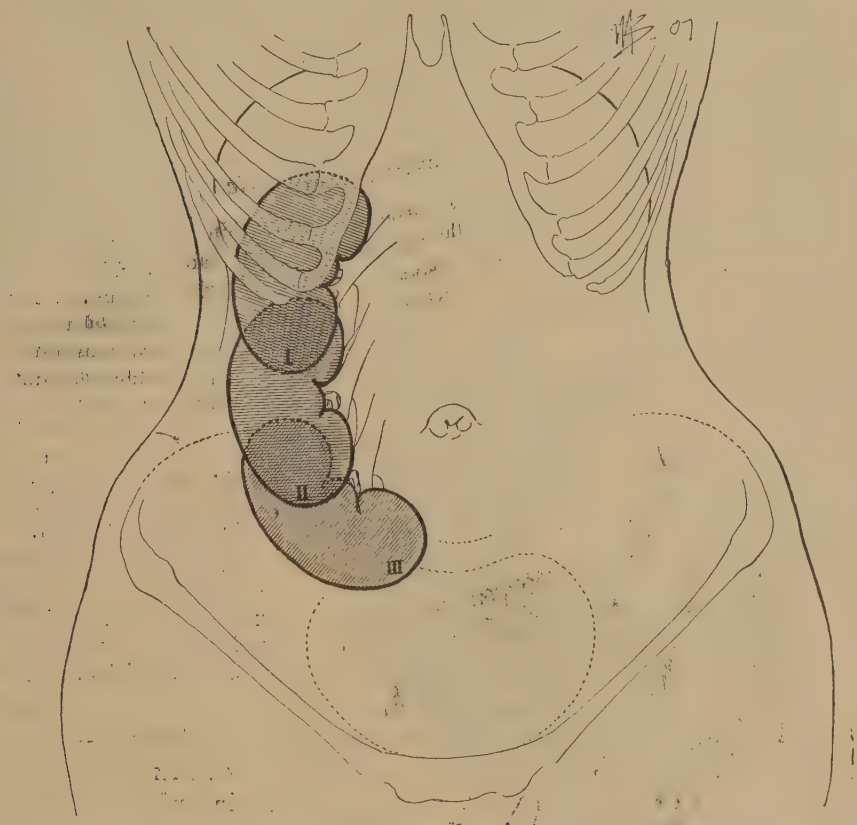

Fig. 476.—Diagrammatic Representation of Three Degrees of Displacement of the Kidney. First Degree (Palpable), Only the Lower Pole is Perceptible to the Touch; Second Degree (Movable), the Upper Pole Just Emerges from Under the Costal Margin; Third Degree (Floating), the Entire Kidney Can Be Palpated. Note How the Vascular Pedicle Suspends the Kidney to a Certain Degree So That in the Second and Third Stage the Kidney Swings Over Toward the Midline of the Body. (After H. A. Kelly and C. F. Burnam.)

pushed downward as far as the groin, or medialward as far as the midline, it is a *floating kidney.*

Diagnosis.—The signs on palpation usually make the diagnosis clear. Occasionally a movable kidney may be confused with other masses (gall-bladder, neoplasms of intestine or ovary).

When Dietl's crises occur, the condition is often falsely diagnosed. It has been mistaken for stone in the kidney, for gall-stone colic, for chole-

cystitis, and even for appendicitis. The pain can often be reproduced between attacks by injection of fluid into the ureter on the same side. A thorium X-ray of the renal pelvis on the two sides may show a slight dilatation on the affected side (hydronephrosis).

(*b*) *Congenital Cystic Kidneys* (*Bilateral Polycystic Kidney*)

Nature.—The kidneys are made up of a number of small, thin-walled sacs, filled with clear yellowish fluid. Between the sacs are islands of fairly normal renal parenchyma. The condition is nearly always bilateral, though unilateral cases have been reported, and some of them have been successfully operated upon.

The cysts are congenital in origin, though the disease may cause no symptoms until after middle life, and then only through failure of renal compensation.

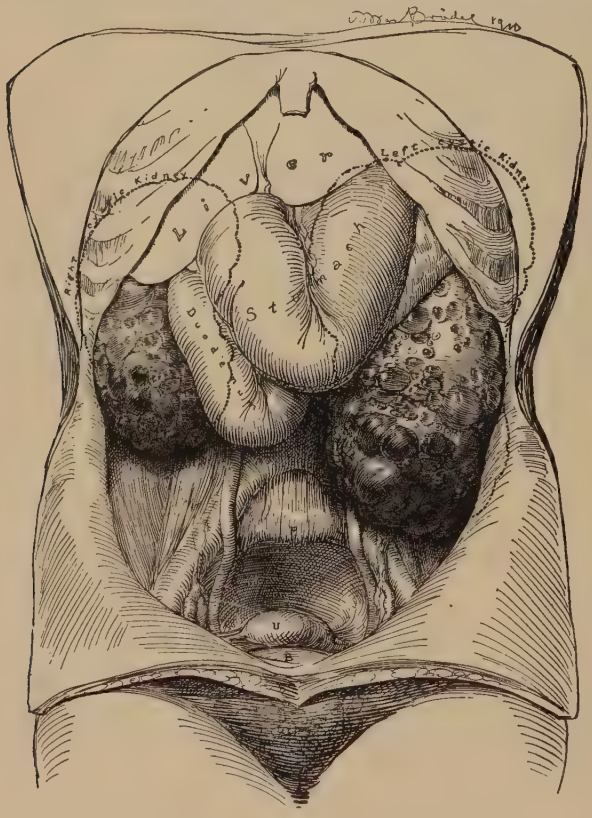

Fig. 477.—Bilateral Congenital Cystic Kidneys in the Adult. (J. H. H., Autopsy No. 1258, March 2, 1900.) (After H. A. Kelly and C. F. Burnam.)

Embryologically, there is a failure of the renal vesicles (which give rise to the kidney tubules) to unite with the outgrowths from the Wolffian duct (which form the renal pelvis). Polycystic kidneys are sometimes associated with congenital cystic disease of the liver and pancreas.

The disease may occur in families. Osler reports an instance in which a mother and her daughter were both afflicted.

Symptoms.—There may be no symptoms at all in early life, and the condition is sometimes found accidentally, through examination of the abdomen for other reasons. Bilateral *masses* are found in the region of the kidneys, and their *nodular surface* at once gives the clew to the nature of the condition. In other instances *hematuria* has occurred, off and on, for years.

Sooner or later the signs of chronic nephropathy, including *polyuria*, *arterial hypertension* and *heart hypertrophy*, gradually develop. Toward

the end of life *uremic symptoms* may appear. Very often *myocardial failure* sets in toward the end. A rare complication is *rupture* of a cyst.

In two cases I have observed very great reduction in the *phenolsulphonephthalein-output* on making this functional renal test. Despite the low output, no uremic symptoms developed, at any rate for months afterward, during which time the patients were under observation.

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3. The Nephropathies of Circulatory Origin

Under this heading we shall describe (1) the *stasis kidney,* or kidney of chronic passive congestion, (2) the *diffuse arteriolar [sclerotic] nephropathy* (primary or genuine contracted kidney), and (3) the *focal atherosclerotic nephropathy,* ordinarily known in the literature as the "atherosclerotic kidney."

(*a*) *The Stasis Kidney*

(*Chronic Passive Congestion of the Kidney*)

Etiology.—This is one of the commonest conditions met with in medical practice, and one that is often misunderstood by physicians, who mistake it for a nephritis. It occurs under all conditions in which there is chronic passive congestion of the organs due to venous stasis; thus, it follows (1) *cardiac decompensation,* no matter what its cause. Less frequent causes of stasis in the renal veins are (2) *obstructions to the inferior vena cava* above the level of the renal veins, and (3) *pressure upon the renal veins* themselves, from any cause.

Experimental work indicates that in cardiac decompensation, two factors play a rôle; (1) feeble arterial flow into the kidney, and (2) lessened venous outflow from the kidney. A *feeble arterial flow* causes cortical, and, especially, glomerular congestion, with excretion of albumin into the capsular space. *Lessened venous outflow* causes engorgement of the medullary part of the kidney. In cardiac decompensation, therefore, the entire kidney is engorged. The kidney becomes somewhat enlarged, of a dark red color, and is firmer than normal (*cyanotic induration*). Degenerative changes occur in the epithelial cells of the renal tubules, but there are no actual inflammatory lesions.

Symptoms.—The *urine* is scanty, the amount being reduced to 400-800 c.c. in the 24 hours. It is of a darker color than normal, and is turbid and concentrated, depositing a brick-dust sediment of urates in the cold. The specific gravity is high. A moderate amount of albumin is present, probably passing out into the urine through the glomeruli. Casts are present, but they are relatively few in number, as there is no marked degeneration or destruction of the renal epithelium. A few red and white blood corpuscles are usually to be found in the sediment.

On making *functional tests,* the phenolsulphonephthalein output is usually reduced, though not to so great a degree as one would suspect in a nephritis with the same degree of albuminuria. Under Methods of Testing Renal Function, a protocol of a case carefully studied after a renal test diet has been given (*q. v.*).

Diagnosis.—The stasis kidney might be mistaken for early nephritis, though when signs of myocardial insufficiency are present (dyspnea, cya-

nosis, edema, palpable and tender liver, enlarged heart, cardiac arhythmia), the probability of the abnormal urinary condition being entirely due to the circulatory insufficiency should always be kept in mind. If cardiac compensation be restored (rest, digitalis, etc.), the urine becomes more abundant, of higher color, and free from protein and casts; should the urine, however, remain abnormal, some other form of nephropathy coexists.

If the renal test diet be given, and the water-intake, the water-output, and the specific gravity be followed as directed these measures will be found helpful for diagnosis.

(*b*) *The Diffuse Arteriolar* (*Sclerotic*) *Nephropathy or Commonest Form of Chronic Nephropathy with Arterial Hypertension and Without Renal Dropsy*

(Primary Contracted Kidney; Genuine Contracted Kidney; Chronic Hypertensive Nephropathy; Often Called Chronic Interstitial Nephritis)

Definition.—A chronic renal atrophy resulting from a diffuse sclerosis of the small organ-arterioles of the kidney (in the sense of Jores), with gradual formation of small red, granular kidneys, which exhibit adherent capsules and a reduction of the renal cortex, and clinically characterized by polyuria, slight albuminuria and cylindruria, and chronic arterial hypertension with heart hypertrophy, death occurring, often after many years of fairly good health, from cardiac failure, cerebral apoplexy, uremia, or a terminal infection.

Etiology and Pathogenesis.—The cause of the arteriolar sclerosis underlying the disease is but poorly understood. Hard work, chronic intoxications (gout, lead, alcohol, alimentary toxins), and minute foci of chronic infection, are among the factors that have been held responsible. The disease is common among those who lead the "strenuous life"; thus, the incidence is large among brokers in Wall Street. I have been impressed, however, with the tendency to occurrence in certain families, and I cannot help but feel that there is a congenital factor, possibly Mendelian, in many of the cases.

On account of the diffuse nature of the process involving the arterioles throughout both kidneys, some poison carried through the blood must, one cannot help thinking, be responsible. A chronic auto-intoxication from the intestine is believed by many to be a cause, and possibly other faults of metabolism leading to intoxication, including intoxications depending upon internal secretion, especially of the chromaffin tissue, may be important etiologically. I have met with the condition not infrequently in association with Graves's disease, though many cases of Graves's disease are, on the other hand, associated with arterial hypotension.

I am inclined to separate this type of hypertensive nephropathy from the hypertensive nephropathy that follows the diffuse non-suppurative interstitial nephritis

of Councilman and the contraction of the kidney that follows exudative and proliferative forms of glomerulonephritis. Such good observers as Klotz and McMeans are, however, doubtful of the validity of such separation, and it must be admitted that the matter is not yet fully settled. We must be ready to change our ideas of pathogenesis and of classification, if further studies prove that present conceptions are in part erroneous.

Fig. 478.—Exophthalmos in Chronic Renal Disease. (After Barker & Hanes, Am. J. M. Sc.)

Attempts to reproduce the disease in experimental animals have not been very successful, though the experiments of Haven Emerson and of E. C. Dickson are suggestive. The bibliography of the experimental work is well reviewed in Sir John Rose Bradford's Croonian Lecture on Bright's Disease.

Symptoms.—The *onset* is very gradual, extending over years. The condition may be first suspected by the finding of a trace of albumin in the urine at an examination made for life insurance. Doubtless, in many cases, the disease has existed a decade or more without exciting suspicions as to its presence, the patient only consulting the physician when signs of cardiac failure, of uremia, or of atherosclerosis have appeared. A careful inquiry in such cases will, however, usually reveal the fact that *polyuria* and *nocturia* have existed for a long time.

As the disease advances the signs of *arterial hypertension* may be prominent, including headache, nose-bleed, matutinal insomnia, dyspnea, or other symptoms of cerebral atherosclerosis. The maximal and minimal blood pressures gradually rise. When the patient is first seen, the systolic pressure may be very high. A blood pressure continuously above 160 or 170, without obvious cause, should always excite suspicion of a developing diffuse renal atrophy. Not infrequently the pressure is over 200 when the patient is first seen, and maximum pressures as high as 300 or higher are sometimes met with in the disease. Gradually *hypertrophy of the heart* develops, especially of the left ventricle ("Traube heart"), the apex being dislocated downward and to the left, and the aortic second sound markedly accentuated. In many cases *symptoms of chronic circulatory insufficiency* develop (dyspnea, enlargement and tenderness of the liver, beginning edema due to myocardial insufficiency).

Edema does not occur in this disease from the renal lesion directly. Should edema be present, it is nearly always due to myocardial insufficiency, though of course a renal edema may result from the superimposition of a nephrosis or of an acute glomerulonephritis upon the chronic arteriolar nephropathy.

If the patient, however, give a history of transient edemas occurring in earlier life, especially in association with some infection or another, one should think of the possibility of the condition being that of secondary contracted kidney (*q. v.*), rather than the primary contraction of the kidney of arteriolar sclerosis.

In the later stages of arteriolar nephropathy *uremia* is very common. The patients begin to have *headaches* and often visual disturbances due to *uremic amaurosis,* or, sometimes, to an outspoken *albuminuric retinitis* with the typical flame-shaped lesions in the retina. Not infrequently these patients first consult the ophthalmic surgeon, and are sent by him to the internist on account of the albuminuric retinitis. Other signs of uremia include *nausea, vomiting, diarrhea,* and, toward the end, *convulsive seizures, delirium,* and *coma.* Cheyne-Stokes breathing is not uncommon in the late stages.

When asked about his *urine,* the patient may assert that he is sure there is nothing wrong with it; that he always urinates freely, and that the urine has no sediment. But this free passage of an abundant pale urine is one of the most significant signs for the physician. The specific gravity is lower than normal (1.005-1.012); it may be very low (1.002-1.005). As long as there is no circulatory insufficiency there may be only a trace of albumin in the urine; indeed, albumin may, at times, be absent altogether. There is very little sediment, though, on centrifugalization, a few hyaline casts will usually be found, and, occasionally, a granular cast.

When the heart begins to fail, edema may appear, with orthopnea, Cheyne-Stokes breathing, and gallop rhythm; the urine then may become scanty, owing to the superimposition of a stasis kidney upon the renal atrophy due to the sclerosis of the arterioles.

Diagnosis.—This is usually easy if the patient be seen before cardiac decompensation has developed. A persistent polyuria, with low specific gravity of the urine, a trace of albumin in the urine with a few hyaline casts, along with chronic arterial hypertension and hypertrophy of the heart, often without any demonstrable thickening of the radial artery, make the diagnosis certain. If the patient be seen for the first time only after cardiac decompensation has set in, there may be temporary difficulty in making the diagnosis, for the symptoms of the arteriolar nephropathy are then masked by those of the superimposed chronic passive congestion; moreover, the attention is then likely to be directed rather to the failing myocardium, without suspicion of the underlying primary cause. After the heart has been strengthened, however, by rest, diet and cardiotonic treatment, and the venous stasis has been overcome, the arteriolar nephropathy will be unmasked.

The methods of functional renal diagnosis should be applied in any doubtful case. In chronic arteriolar nephropathy we usually find the typical vascular hyposthenuria of Schlayer, with evidence of marked sensitiveness of the renal vessels to diuretic stimuli. In the early stages of

the disease, and when there is no cardiac decompensation, the phenolsulphonephthalein output may be only slightly, if at all, reduced, but in the later stages of the disease, or during periods of cardiac decompensation, or when an acute nephropathy is superimposed upon the chronic process, an outspoken reduction of the phenolsulphonephthalein output will be found.

In chronic arteriolar nephropathy, too, the lactose test is a valuable sign. There is nearly always some delay in the excretion of lactose on making the functional test.

If the general practitioner would remember that a persistently high blood pressure, without apparent cause, especially in middle-aged people, is most often due to this form of arteriolar nephropathy, that is, to beginning contraction of the kidneys, many mistakes would be avoided and many patients could be put upon a régime that would keep them in comparative health for a long period.

Let me make myself perfectly clear. The sclerosis of the arterioles is a process that seems to involve the viscera all over the body; the contraction of the kidneys is incidental to the diffuse involvement of the renal arterioles.

The differentiation of the disease from the secondary contracted kidney may be difficult or impossible during life, unless the earlier history of the patient be known. If a clear history of preceding acute nephritis with edema, or of a preceding chronic glomerulonephritis, can be obtained, the case may be recognizable as probably one of secondary contraction of the kidney. In the end stages, however, the symptoms are practically identical in the two conditions, and, as far as the patient is concerned, it is a matter of indifference which of the two exists, except that the outlook is less favorable, as far as length of life is concerned, in the secondary contracted kidney than in the primary form.

Finally, some of the worst forms are met with in patients in whom there is a combination of a true chronic nephritis (with secondary contraction) with an arteriolar nephropathy (with primary contraction).

(c) *The Focal Form of Atherosclerotic Nephropathy*

(Senile Atherosclerotic Kidney of Ziegler)

Nature, Etiology and Pathogenesis.—Here we have to deal with what is ordinarily called the "atherosclerotic kidney." At autopsies on such cases the kidneys may be of normal size; they may be slightly enlarged, or they may be slightly reduced in size. They are firmer than normal. Scattered over the kidney are seen areas of depression, corresponding to localized or patchy atrophy due to atherosclerotic disease of the vessels supplying the part. The striking difference, however, between this process and that of the arteriolar nephropathy described above, lies in the fact that in the local form, we have to deal with a process involving certain only of the renal vessels, and often those of larger caliber, usually in association with general atherosclerosis of the peripheral vessels over

the whole body, while in the arteriolar nephropathy we have to deal, as we have seen, with diffuse involvement of the small organ arterioles throughout both kidneys, leading, not to a "patchy atrophy," but to an atrophy evenly distributed throughout each of the kidneys, and frequently associated with similar arteriolar disease in the other organs of the body, though, even then, often without the signs of atherosclerosis in the larger peripheral vessels, such as the radial artery.

The *etiology* in the focal form of atherosclerotic nephropathy is that of atherosclerosis in general, about which we do not know nearly as much as we should like to know.

Symptoms.—The *urine* may show a trace of albumin, but it is often free from albumin for long periods. There is generally some polyuria, and the specific gravity may be normal, or a little less than normal. At times it is higher than normal. The sediment contains a few hyaline casts, especially if the centrifugalized sediment be studied. Errors in diet, exposure to cold, alcoholic excesses, or slight infections, may cause the appearance of a little albuminuria and increase the number of casts. A few red corpuscles can nearly always be demonstrated in the urine if the centrifugalized sediment be examined microscopically.

On *functional renal diagnosis* the phenolsulphonephthalein output may be normal, and the kidney may, for a long time at least, be able to excrete a concentrated urine. The blood pressure may be normal, but it is usually somewhat higher than normal. In some cases the blood pressure is lower than normal.

Diagnosis.—The slight polyuria, the cylindruria, the transient albuminuria, the peripheral atherosclerosis (thickened radial), and the signs of atherosclerosis elsewhere in the body, permit one often to make a probability diagnosis, though in many cases the condition is not discovered until autopsy. In this patchy form of arteriosclerosis of the kidney renal decompensation rarely occurs, unless there is cardiac decompensation from some cause or a complicating acute infection. The condition is benign in contrast with the gravity of the diffuse arteriolar sclerotic kidney described above.

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4. Toxic Degenerative Tubular Nephropathies Without Marked Glomerular Involvement (The So-called Nephroses)

Under this heading we shall consider a large group of cases in which there is evidence, clinically and at autopsy, of degeneration of the tubular epithelium, though the glomeruli may remain practically intact. They are usually acute processes, though the amyloid kidney is a chronic process. Among them we may consider, (1) the slight tubular nephropathy of acute infectious processes (or the so-called febrile albuminuria), (2) the kidney in sublimate intoxication, (3) the kidney in chrome intoxication, (4) the kidney of pregnancy, (5) the kidney in other intoxications, and (6) the amyloid kidney.

(*a*) *Slight Toxic Nephropathy of Acute Infections*

(*Febrile Albuminuria*)

In almost any acute infection with fever, there is a slight albuminuria, and a few casts may appear in the urine. The whole condition clears up when the infection is over. This *febrile albuminuria* is not of grave significance, and does not indicate an actual nephritis, but only a parenchymatous degeneration of the epithelial cells of the tubules. It includes what is known to the pathologist as cloudy swelling, on the one hand, and certain demonstrable degenerative changes in the epithelium (hyaline, granular, fatty), on the other. It is to be sharply distinguished from the acute glomerulonephritis that sometimes complicates acute infections.

(*b*) *The Kidney in Sublimate Intoxication*

In corrosive sublimate poisoning, there may be extensive degeneration of the renal epithelium, with albuminuria and cylindruria. The epithelium of the tubules may become necrotic, and casts composed of dead epithelial cells may be thrown off. The condition is a diffuse one, and uremic symptoms may develop, with increase of blood pressure, though it is uncommon to have edema. The patients may die in uremia, but if they survive the poisoning, for the condition is largely reparable, the renal epithelium may regenerate and more or less complete recovery follow.

(*c*) *The Kidney in Chrome Intoxications*

In poisoning with bichromate of potash, with chromic acid, and with other chrome preparations, a similar toxic degenerative change may occur in the epithelium of the renal tubules. Here, too, if the intoxication be survived, more or less complete recovery may follow, with regeneration of the renal epithelium.

(*d*) *The "Kidney of Pregnancy" or the Pregnancy Nephropathy*

Occurrence.—It is known by every general practitioner that renal disease is a frequent complication of pregnancy, often associated, near term or afterward, with eclampsia. As soon as pregnancy is believed to exist, the urine should be carefully examined, for it is very important to know, when a nephropathy exists in the latter stages of pregnancy, what the condition of the urine was in the early stages. Thus the patient may have suffered from a chronic nephropathy before pregnancy, and, if so, this is likely to undergo marked exacerbation during the period of pregnancy. If the urine be normal at the beginning of pregnancy, it should be examined at intervals throughout the period of gestation, and the appearance of albumin or of casts should be regarded as probably due to the development of the "kidney of pregnancy," and as an indication for the greatest care and the ordering of special protective measures. It seems clear now that the typical "kidney of pregnancy" is a *toxic tubular nephropathy without glomerular involvement,* and often, though not always, without any subjective symptoms of toxemia.

Symptoms.—When the "kidney of pregnancy" develops, albumin and casts appear in the urine; the amount of urine is reduced, and the specific gravity is higher than normal. The urea-content of the urine may be diminished, though the ammonia-output is usually high, an indication of acidosis. Edema often develops, and it is important to try to make out, if edema occur, whether it is due to the intra-abdominal pressure, or to a renal involvement. Uremic symptoms are common, the patients complaining of insomnia, headache, vertigo, dimness of vision, nausea, and vomiting. Such symptoms are of the greatest importance, for they are often the harbingers of an eclamptic seizure.

It is interesting that when pregnancy is terminated, either naturally or artificially, the kidney of pregnancy usually clears up promptly. It would seem as though some toxic substance, either of maternal or fetal origin, originates in the uterus and causes the tubular nephropathy.

Diagnosis.—When albumin and casts appear in the urine during pregnancy, or when edema or uremic symptoms develop while a pregnancy is in progress, the physician must try to determine whether he is dealing with the toxic tubular nephropathy known as the "kidney of pregnancy" or with some other form of nephropathy. Thus, if albumin and casts have been present before pregnancy began, or if the patient shows cardiovascular changes with hypertension or an albuminuric retinitis, it is probable that we are not dealing with the simpler toxic nephropathy of pregnancy, but with another nephropathy. An acute glomerulonephritis, developing during pregnancy, will be hard to differentiate from the typical kidney of pregnancy, though hematuria and abundant casts speak in favor of an acute glomerulonephritis. Sometimes the diagnosis can be made in retrospect, for if the urine clear up promptly on emptying the uterus, with rapid disappearance of the toxic symptoms, the condition was probably the kidney of pregnancy, whereas, if the convalescence be slower, or incomplete, it is likely that an acute glomerulonephritis, or some other form of nephropathy, existed.

When uremic convulsions occur with the "kidney of pregnancy," about a quarter of the women die. The outlook for the child is still graver.

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(e) *Other Toxic Degenerative Tubular Nephropathies*

A whole series of other toxic substances can give rise to a degenerative tubular nephropathy without marked involvement of the glomeruli. Fortunately, all these nephropathies can be studied in experimental animals, and much light has been thrown, in recent years, upon the pathology of the kidney by such experimental work.

Experimental studies with *chromates* and *corrosive sublimate* produced almost pure tubular lesions. Experimental intoxications with *arsenic, cantharidin* and *venom* produce almost pure glomerular lesions and pure glomerulitis, while intoxications with *uranium nitrate* cause both tubular and glomerular lesions, though the tubular epithelium is predominantly involved.

Studies controlled by the application of functional, as well as of histological, methods have modified the views formerly held regarding the effects of individual poisons. Thus, Takayasu has shown that there may often be severe disturbance of function of a part of the kidney when there is little or no evidence of histological lesion there. Schlayer and his pupils in Romberg's clinic have tested the different forms of experimental nephritis by means of functional methods, and American investigators (Christian, Fischer, MacNider, Mosenthal, and others) have also used functional tests in the experimentally produced diseases.

(f) *The Amyloid Kidney*

(Waxy Degeneration; Lardaceous Degeneration)

Definition.—A nephropathy in which a peculiar substance known as "amyloid" is deposited in the kidney, chiefly in the walls of the blood vessels, sometimes in the membrana propria of the renal tubules, similar deposits occurring in other organs (liver, spleen, intestine, etc.).

Etiology.—Amyloid deposit is known to occur chiefly in cachectic states, due to chronic pyogenic infections, syphilis or tuberculosis. Some substance circulating in the blood must be responsible, since the amyloid disease is not limited to any one organ, but appears simultaneously in several.

Among the chronic suppurations in which amyloid is prone to occur may be mentioned chronic osteomyelitis, chronic empyema, chronic suppurative pyelitis, and bronchiectasis; furthermore, in chronic tuberculosis of the lungs, bones and joints, amyloid is common, and in tertiary syphilis it is frequently seen. It has been reported occasionally in a number of other conditions. Amyloid is far less common at autopsy than formerly because of the earlier recognition and the better treatment now of chronic suppurative processes, of tuberculosis, and of lues.

When amyloid degeneration occurs in the kidney, the organ enlarges and the cortex broadens and grows waxy-looking. On section, the glomeruli stand out

like "glistening dewdrops." If a little Lugol's solution be poured over the surface, the glomeruli and the walls of blood vessels and of tubules that contain the amyloid material stain a dark, mahogany-brown color.

Symptoms.—If the signs of a renal disease (albuminuria, cylindruria), with edema, but without cardiovascular changes, occur, in association with enlargement of the spleen and liver, and in the presence of some condition that could provoke amyloid deposits (chronic suppuration, tuberculosis, lues), there can be but little doubt as to the condition. Mild cases, however, and even many of the severer forms, are not recognized until autopsy.

It is to be remembered that amyloid disease can be implanted upon a kidney that is already the seat of some other form of renal disease (*e. g.*, arteriolar nephropathy).

Diagnosis.—Leube's rules that "amyloid kidney is to be diagnosed only (1) when the liver and spleen, or at least one of them, especially the spleen, are enlarged and hard, (2) when at the same time one of the recognized causes of amyloid is present, (3) when the urine, though abundant and of low specific gravity, is clear, with but little sediment, and yet rich in albumin, and (4) when the cardiac and vascular phenomena of contracted kidney are absent," still hold good.

It is interesting to recall that the *blood pressure* is usually low in amyloid disease of the kidney, even in the cases that are not of tuberculous origin. In three cases that occurred recently in Bogg's service at Bayview Hospital the blood pressure was low; in one case the maximal systolic pressure was at times as low as 70.

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5. The True Inflammatory Nephropathies, or the Nephritides

Under this heading we shall include (1) the different forms of acute, subacute and chronic nephritis, and (2) the specific forms of nephritis due to tuberculosis and to lues.

(*a*) *Acute Nephritis*

Definition.—An acute inflammation of the kidney. I do not include, as many do, the toxic-degenerative tubular nephropathies, or nephroses, under the term nephritis. The term acute nephritis, as used in this volume, includes (1) acute diffuse glomerulonephritis, (2) acute focal glomerulonephritis, and (3) acute interstitial, non-suppurative nephritis.

i. Acute Diffuse Glomerulonephritis

(*Acute Inflammatory Nephropathy with Edema*)

Definition and Etiology.—The disease follows, most often, exposure to cold, or some infection, especially *streptococcus infection* (tonsillitis). It seems likely that a toxemia from a streptococcus infection, without actual localization of the streptococci in the kidney, can cause the disease, though, in other cases, an actual diffuse localization of the streptococci within the kidneys themselves doubtless occurs. Microörganisms other than streptococci, or their toxins, may sometimes be responsible.

The acute nephritis following scarlet fever is one of the best known examples of acute diffuse glomerulonephritis. Whether it is due to the unknown virus of scarlet fever itself, as seems most likely, or to a complicating streptococcus infection or streptococcus intoxication, is not certainly known.

The "febrile albuminuria" of acute infections is not included here under the designation acute nephritis, but under this term we do *include* the definite, outspoken, acute glomerulonephritis that sometimes occurs as a complication in typhoid fever, pneumonia, smallpox, cholera, yellow fever, malaria, and many other acute infections.

Acute nephritis is more common in young people than in the middle-aged and older people. Males are more often affected than females.

Symptoms.—The onset may be sudden, with edema, pallor, headache, digestive disturbances, oliguria, albuminuria, hematuria, and cylindruria. Or it may be insidious, and be discovered only on routine examination of the urine in the course of some other disease.

As a type of the **acute nephritis with abrupt onset,** we may take *scarlatinal nephritis,* which so often develops during convalescence from that disease, after the febrile albuminuria of the early stage of the affection has passed off. From the very beginning the three main features of this form of nephritis are usually observable; namely:

(1) The quickly developing *edema,* with puffy eyelids, pasty face, watery eyes and lumbar pad.

(2) The marked *changes in the urine* (outspoken oliguria, pollakiuria, hematuria, high specific gravity, marked albuminuria and cylindruria, increased molecular concentration and electrical conductivity, owing to the lessened excretion of water, though the total solids eliminated in the 24 hours are diminished); and

(3) Definite *uremic manifestations* (nausea, vomiting, urinous odor to the breath, headache, drowsiness, and, sometimes, convulsions and coma).

Other symptoms that may be present include fever (100°-102°), tachycardia or occasionally bradycardia, a rise in the systolic blood pressure, dryness of the skin with pruritis, and secondary anemia.

The *course* of the disease is variable. The edema may become outspoken, giving rise to a general anasarca, but sometimes there is much less edema, or only a little fugitive edema. In a few cases edema has appeared before albuminuria or casts were present in the urine. Edema of the glottis and edema of the lungs are dangerous complications. After a few days the urine may become more abundant and less smoky. An early increase in the output is a good sign. The albumin and casts then slowly

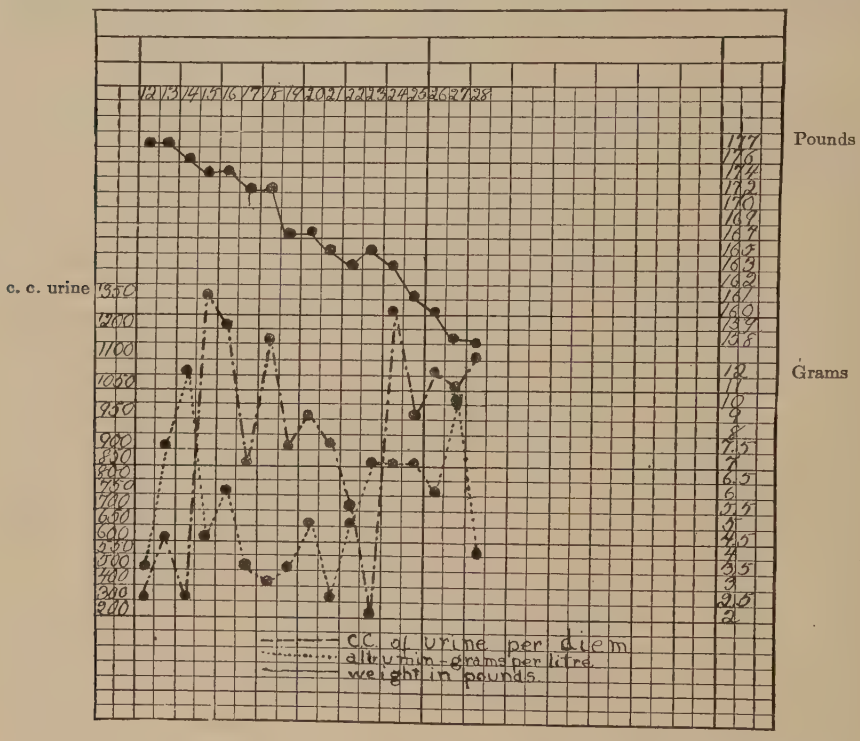

Fig. 479.—Acute Nephritis—Chart Showing Daily Output of Urine, Albumin per Liter, and Loss in Weight as the Edema Disappeared. (Miller and Hegeman, Med. Clinic, J. H. H.)

disappear from the urine, though showers of casts and an increase in the albumin may be observable from time to time for several weeks. The uremic symptoms vary greatly in their severity, sometimes being so mild as not to attract attention. In other instances the intoxication is so severe as to cause death from uremic poisoning (convulsions, coma).

As a type of the **acute glomerulonephritis of insidious onset,** we may take the *form that sometimes complicates typhoid fever or lobar pneumonia.* Here the onset may be so gradual as not to be noticed unless daily routine examinations of the urine are made. There may be no edema, and no uremic phenomena may appear in the milder cases. The symptoms of the nephritis are so trivial that they are lost sight of in the pres-

ence of the marked symptoms of the primary disease. In typhoid fever the acute nephritis may usher in the disease, in which case we have the so-called *nephrotyphus* or *renal typhoid*. It is more common, however, to have a complicating acute nephritis later on in the course of typhoid fever or during convalescence.

It seems unnecessary to describe the acute nephritis that occurs in the course of *other infections* (malaria, diphtheria, influenza, smallpox, measles, rheumatic fever, Asiatic cholera, etc.). They conform more or less in type to the nephritis that complicates typhoid fever, though in each infection there may be certain peculiarities. Much has yet to be learned regarding the precise etiology of these forms of acute nephritis complicating the various infectious diseases.

Diagnosis.—In the acute nephritis of abrupt onset (*e. g.*, scarlatinal nephritis), there can scarcely be any doubt as to diagnosis. It is in the forms with insidious onset that the disease is most often overlooked.

If the condition of the patient before the onset of the nephritis has been known, and especially if the physician possess a knowledge of the state of the urine previously, the changes in the character of the urine will inform him as to the nature of the trouble he is dealing with.

In the **differential diagnosis** of acute nephritis, we must distinguish it (1) from *simple febrile albuminuria;* (2) from *orthostatic albuminuria;* (3) from *chronic passive congestion* of the kidney (stasis kidney); (4) from *subacute or subchronic glomerulonephritis* (sometimes called chronic parenchymatous nephritis); (5) from *amyloid kidney;* (6) from *renal infarct;* (7) from the different forms of *pyelitis;* and (8) from *renal tuberculosis.*

In estimating the damage that has been done to the kidney and the relative injury to the glomeruli, on the one hand, and to the tubules, on the other, the methods of *functional renal diagnosis* may be resorted to, especially the giving of a renal test diet, in association with the following of the water-intake and water-output, the specific gravity of the urine, the phenolphthalein-output, the lactose-excretion, and Ambard's coefficient or McLean's index. The effects of diuretics (theocin, diuretin, NaCl) should, if tested at all, be very cautiously tried.

ii. Acute Focal Glomerulonephritis

(*Acute Nephropathy with Slight Hematuria without Edema*)

We are gradually becoming familiar with forms of focal glomerulonephritis and of embolic focal nephritis, in which there is evidence that only minute disseminated areas in the kidneys are involved, the rest of the kidney structure remaining intact. These cases depend apparently upon the lodging of infective emboli, often of low grade, in the kidneys. One of the best known forms is the embolic glomerulitis studied by Baehr in endocarditis lenta, in which single glomerular capillaries may be thrombosed, or the site of embolic lodgment.

In these cases of focal nephritis there may be no symptoms referable to the kidney, except the changes in the urine (albuminuria; microscopic hematuria). Uremic symptoms do not develop, since a great deal of healthy kidney tissue remains. As a rule, edema does not occur, though fugitive edemas are sometimes observed. There is no increase of the blood pressure contrary to what is met with in the diffuse forms of nephritis.

When septic emboli reach the kidney and cause an embolic focal nephritis, *miliary abscesses* may occur in the kidney. These are met with, for instance, in general staphylococcus septicemia. In such cases, the disease is, ultimately, almost uniformly fatal (general sepsis).

iii. Acute, Interstitial, Non-suppurative Nephritis

This form of nephritis, found, sometimes, at autopsy after scarlet fever, or after acute rheumatic fever, has been especially studied by the pathologists. Aggregations of round cells are observable in the interstitial tissue of the kidney. The glomeruli and the tubules remain almost uninvolved. The condition is scarcely recognizable *intra vitam,* since it may yield no symptoms that point to the kidneys. It is possible that this form of acute nephritis may be the forerunner of chronic interstitial changes later.

This form of kidney has been very carefully studied by Councilman, and he and Klotz think it probable that some of the small red granular kidneys associated with arterial hypertension are to be regarded as sequelae of this form of nephritis.

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(*b*) *Chronic Nephritis*

i. Subacute and Subchronic Nephritis with Edema

(Subacute or Subchronic Diffuse Glomerulonephritis, Chronic Parenchymatous Nephritis, Large White Kidney)

Definition.—A diffuse inflammation of the kidney, involving marked changes in the parenchyma (glomeruli and tubules) and, to a less extent, in the interstitial tissue of the kidney, characterized clinically by marked urinary changes, edema, secondary anemia, and, usually, a fatal termination in one or two years.

Pathology.—The disease is subacute or subchronic, running its course usually in one or two years. It is a diffuse process, not a focal process, and while the lesions are predominantly parenchymatous, they are never limited solely to the parenchyma, but involve also the interstitial tissue. At autopsy, the *large white kidney* of Wilks is most often found, though the *large mottled* or *variegated kidney* may be seen, in which areas of hemorrhage, or of hyperemia, alternate with areas of fatty degeneration and of anemia.

On *microscopical examination of the kidney,* extensive degenerative changes are observable in the renal epithelium, especially in the secretory portions of the *tubules.* Many of the tubules contain casts and red and white blood corpuscles. The *glomeruli* are enlarged. There is degeneration of the capsular epithelium, and there may be nuclear multiplication in the glomerular tuft, either in the endothelial cells of the capillaries, or in the connective tissue cells between them. *Hemorrhages* into the capsular space, and desquamation of capsular epithelium into the capsular space, are often observable. There is some *edema* of the interstitial connective tissue, and areas of round celled infiltration may be met with.

Most of the patients die while the kidney is still large. In a few instances, there is a gradual improvement in the symptoms, and secondary contraction of the kidney, due partly to true chronic interstitial nephritis, and partly to atrophy of the degenerated secretory elements, occurs. The kidney that has undergone secondary contraction is the so-called *small white kidney,* in contrast with the small red granular kidney or primary contracted kidney of the arteriolar nephropathy already described. This secondary contracted kidney may not be smaller than the normal kidney, though it is much smaller than the large white kidney from which it results.

Etiology.—The cause is not definitely known. In all probability, the etiology is variable. Most often recurring streptococcus infection and intoxication seems to be responsible. It is probable that the *Streptococcus viridans* is the etiological agent in many of the cases. Alcoholism and lues predispose.

Symptoms.—The onset is insidious, with anemia, edema, and characteristic changes in the urine.

The *edema* may be very slight at first—a little puffiness of the eyelids in the morning or of the ankles at night. Gradually, however, the edema increases, and the most extreme cases of anasarca are met with in this form of nephritis. There is not only involvement of the subcutaneous tissues all over the body, but dropsy of the serous cavities also develops. As a result of the combination of edema with secondary anemia and with hydremia, a characteristic, puffy, pasty appearance to the face develops, so well known to the experienced physician that he can pick out instances of the disease on walking down a hospital ward.

The *urinary changes* in this disease are striking. There is marked oliguria, but, despite this, the specific gravity may be practically normal, or it may be lower than normal. The urine is high colored and shows an abundant sediment, consisting of casts, white and red blood corpuscles, renal epithelium, and urates. Albumin is present in large amounts, especially during the day (0.5-2 per cent). The total output of urinary solids is diminished, and there is especially a diminution in the output of chlorids, as this is one of the forms of "hypochloruric nephropathy."

Uremic intoxication of greater or less degree is nearly always present, though the symptom of edema is more striking than are the symptoms of uremia as a rule. The uremic phenomena most often met with consist of headache, drowsiness and digestive disturbances. It is only occasionally that one sees the severer uremic manifestations, such as convulsions, coma, and uremic amaurosis. There is moderate increase of the blood-pressure and slight cardiac hypertrophy. In the early stages the kidney still possesses the ability to concentrate; in other words, a typical hyposthenuria is not present, but in the terminal stage, when the kidney undergoes secondary contraction, an inability to concentrate appears, and the blood-pressure may then become much higher.

Diagnosis.—The presence of albuminuria, hematuria, cylindruria, and oliguria, along with marked edema, in a patient without cardiac decompensation, makes the diagnosis of glomerulonephritis certain. The only difficulty lies in deciding whether we have to deal with (1) the *subacute or subchronic diffuse glomerulonephritis* here under consideration, or with (2) an *acute diffuse glomerulonephritis,* or with (3) an *acute nephropathy superimposed upon a chronic arteriolar sclerosis of the kidney.* The history of the case, and especially the physician's knowledge of the previous condition of the patient and his urine, will be decisive. In the absence of such knowledge there may be real difficulty for a time in arriving at a satisfactory conclusion. Hematuria is rather more marked in acute nephritis than in the subacute form, but occasionally outspoken hemorrhages occur, even in this form.

There should be no difficulty in distinguishing the disease under con-

sideration in its subacute or subchronic stage from either the *primary contracted kidney* or the *secondary contracted kidney*, for the marked albuminuria, the large number of casts, the marked edema, the slight cardio-vascular changes, and the moderate increase in the blood-pressure are in marked contrast with the conditions in contraction of the kidney, in which the absence of edema, the polyuria, the small amount of albumin, the few casts, the extensive cardio-vascular changes and the outspoken arterial hypertension are characteristic.

The disease is sometimes confused with *amyloid kidney*, but this confusion will scarcely occur if the criteria for the diagnosis of amyloid, already described, be kept in mind. Similarly, there should be no difficulty in distinguishing the disease from *stasis kidney*.

Whenever possible, *tests of renal function* should be undertaken, as they throw much light upon the state of renal compensation or decompensation, and upon the relative degree of injury to the glomeruli, on the one hand, and to the tubules, on the other.

ii. Secondary Contraction of the Kidney following Chronic Glomerulonephritis

(Small White Kidney)

This is the end stage of the disease just described, and its main features have already been discussed.

As far as the effect upon the body as a whole is concerned, it closely resembles that of the primary contracted kidney, though in the absence of general arteriolar disease, the other organs of the body may not be so much involved as in the arteriolar nephropathy.

One of the worst combinations met with, however, is the occurrence of a chronic diffuse glomerulonephritis in association with a chronic arteriolar nephropathy. Such combinations do occasionally occur and are very malign.

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(*c*) *The Specific Forms of Inflammatory Nephropathy*

Under this heading we shall take up (a) *tuberculosis* of the kidney, and (b) *lues* of the kidney.

We must distinguish sharply, however, between the *ordinary forms of nephritis* that occur in association with tuberculosis and lues, on the one hand, and *true tuberculosis* and *true lues of the kidney,* on the other. Ordinary diffuse glomerulonephritis is not uncommon in association with tuberculosis and with lues. Whether or not the toxic substances produced in the tuberculosis or the luetic infection are responsible for this, or whether they simply pave the way for the action of the ordinary etiological factors of diffuse glomerulonephritis, we do not know. An interesting feature of the ordinary forms of nephritis developing in association with tuberculosis is the *absence of cardiac hypertrophy.*

i. Tuberculosis of the Kidney

Forms.—Two forms of the disease occur: (1) a *miliary tuberculosis* of the kidneys, which is merely part of a general miliary tuberculosis; and (2) an extensive *local renal tuberculosis,* in which the tuberculous process is not general through the body, but may be mainly confined to the urogenital apparatus. Clinically, miliary tuberculosis of the kidney is of no especial practical interest, but in chronic localized tuberculosis of the kidney it is exceedingly important to make an early diagnosis, as some of the most brilliant successes of modern medicine have been achieved in this field.

Etiology.—The disease at the beginning is practically always *unilateral,* not bilateral. Formerly it was supposed to be associated with genital tuberculosis. This has been shown to be erroneous.

Tuberculosis of the kidney is almost always dependent upon a *hematogenous* or *descending infection.* A few bacilli probably go over into the blood from some local infection elsewhere (*e. g.*, a lymph gland). In rare cases an *ascending* or *urogenous infection,* or an *infection by continuity* from some adjoining focus, may occur. George Walker's studies upon experimental tuberculosis in rabbits show how rare it is to have infection of the kidney by the ascending route. We must now believe that *the urinary organs are only rarely affected from the genitalia,* though it has been proved that tuberculosis of the kidney and of the genital apparatus

may occur together without extension from one to the other, in which event they both, doubtless, had a hematogenous origin.

The *primary source of the infection* may be in a local tuberculous focus (lymph gland, carious bone, apical pulmonary tuberculosis, intestinal tuberculosis). Some *local predisposition of the kidney* may be present (inheritance, local inflammations, local malformations).

The disease occurs most often in the third and fourth decade, though it may occur at any *age*. Both sexes are affected, though the disease is about twice as frequent in *women* as in men.

Pathologists have described several forms, according to the part of the kidney predominantly involved. A descending infection of the ureter and of the bladder develops in the cases not operated upon early.

In the cases that come to autopsy, bilateral involvement is present in more than one-half, but this is because the disease has existed for a long time. Clinical studies indicate a unilateral involvement in about 90 per cent of the cases, at any rate at the beginning. The *right* kidney is slightly more often affected than the left.

Symptoms.—We make the diagnosis of tuberculosis of the kidney upon (1) *urinary changes,* (2) *local swelling* and *pain,* and (3) *constitutional disturbances.*

The earliest sign is *pollakiuria,* with burning or cramplike *pain* about the middle of the flow; this pain increases until the end of urination, but ceases as soon as the bladder is completely emptied. *Nocturia* and *nocturnal polyuria* may be prominent symptoms at the beginning. While the bladder is sometimes involved early, pollakiuria may occur in the entire absence of involvement of the bladder. The urine in renal tuberculosis is *acid* in reaction. There is *albuminuria,* and, on microscopical examination, red and white blood corpuscles can usually be found, though when the ureter on the diseased side is temporarily blocked there may be no urinary sediment at all.

A most important diagnostic sign is the demonstration of *tubercle bacilli* in the sediment. In the absence of general miliary tuberculosis, or of an active tuberculous process elsewhere in the body, the finding of tubercle bacilli in the urinary sediment practically always means a chronic renal tuberculosis. *Tubercle bacilli can certainly be found in the urine in over half the cases if they be carefully sought.* The method of ruling out smegma bacilli and other acid-fast bacilli has been described under Methods of Examination (*q. v.*).

In addition to the microscopic hematuria above mentioned, *intermittent macroscopic hematuria* is an important sign when it occurs. It is often met with in the early stages of the disease, and may be followed by the appearance in the urine of *blood casts of the ureter.* Hyaline and granular casts are, also, not infrequently present.

Local *swelling* or *pain in the kidney* on the side affected may be pres-

ent, though the absence of these symptoms does not by any means rule out a tuberculous process in the kidney. Sometimes a röntgenogram will show an enlargement of the affected kidney.

Among the *constitutional disturbances,* present in the later stages of the disease, the following may be mentioned: impairment of the general health, anemia, fatigability, emaciation, dyspnea; sometimes there is fever, with chills and profuse sweats. Symptoms of indigestion may be prominent, and may, for a time, attract therapeutic interest without exciting suspicion as to their real cause.

The *course* of the disease is essentially chronic, developing slowly over months or years. In cases not operated upon, death sooner or later occurs from cachexia, from complicating infections, from tuberculous disease of other organs, or from amyloid.

Diagnosis.—There is scarcely any other process in which an early diagnosis is more important for the welfare of the patient. Since the disease is nearly always unilateral at the beginning, is almost exclusively hematogenous in its origin, and can be cured by early operation, early recognition is essential. No case should be permitted to go unrecognized until the bladder becomes infected or until the general health has been seriously impaired.

Now that it is a rule that routine urinary examinations shall be made in every patient who consults a physician, the disease is less likely to be overlooked than formerly, especially in patients with a family history of tuberculosis, or in individuals who, themselves, have earlier had signs of a tuberculous infection in some part of the body. When in such individuals pollakiuria, dysuria, polyuria or hematuria appear, we should always suspect a beginning renal tuberculosis; we should examine the urinary sediment carefully for tubercle bacilli (in stained smears and by animal inoculations), and we should early resort to cystoscopic examination and to ureteral catheterization, so as to make comparative studies of the urine obtained from each of the two kidneys. In some cases it may be desirable to make use of a diagnostic tuberculin test. As T. R. Brown emphasizes, it is "good practice to look for tubercle bacilli in every acid, 'sterile,' purulent urine, and to suspect renal tuberculosis in cases of slight urinary disturbances or of constitutional disturbances with no apparent cause."

For a positive diagnosis the finding of tubercle bacilli in the urinary sediment is essential. In women the palpation of a thickened ureter by vaginal examination is important.

For early diagnosis, undoubtedly, cystoscopy with ureteral catheterization is of great help.

When renal tuberculosis is uncomplicated there is usually a leukopenia

and a low systolic blood pressure—points that are helpful in the differential diagnosis.

In the **differential diagnosis,** we must distinguish renal tuberculosis (1) from *pyelitis* or *pyelonephritis due to pyogenic bacteria;* (2) from *nephrolithiasis;* (3) from *hypernephroma;* and when hematuria is present, (4) from *contracted kidney;* (5) from *renal cancer;* and (6) from *other forms of hematuria.*

ii. Syphilis of the Kidney

(Renal Lues)

Two forms occur: (1) a diffuse luetic nephritis; and (2) gumma of the kidney. We can rarely make more than a probability diagnosis when signs of nephropathy develop in association with known lues or when a positive Wassermann reaction coexists. For we must remember (1) that the nephropathy may not be due to the lues, but may be merely associated, and (2) that an amyloid kidney is not uncommon in lues. Marked benefit from antiluetic therapy may help to confirm a probability diagnosis.

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6. Diseases of the Pelvis of the Kidney

Under this heading we shall include, (1) pyelitis; (2) pyelonephritis; (3) hydronephrosis; and (4) nephrolithiasis.

(a) *Pyelitis and Pyelonephritis*

Definition.—By a *pyelitis* is meant an inflammation of the pelvis of the kidney; if the inflammation involve the pelvis of the kidney and also the kidney substance, it is a *pyelonephritis.*

Etiology.—Pyelitis is always due to infection. The bacteria most often concerned are: (1) *Bacillus coli* and (2) *Bacillus tuberculosis.* But any one of several other bacteria may occasionally be met with as the etiological factor (*Streptococci, Staphylococci, Bacillus proteus vulgaris, Bacillus typhosus*).

The infection of the pelvis of the kidney may be either hematogenous or urogenous in origin; rarely it occurs by *contiguity.* In *hematogenous infection* with *Bacillus coli,* this bacillus may have gained entrance through the intestinal wall. Hematogenous infection with *Bacillus tuberculosis* results from tubercle bacilli

that have gotten into the blood from some local focus of tuberculosis elsewhere in the body.

In *urogenous* or *ascending infection,* the pyelitis is usually secondary to a cystitis, which, in turn, often depends upon an infection following catheterization. Any obstruction to the outflow of the urine predisposes to infections of the urinary passages, both cystitis and pyelitis. The urogenous, or ascending, infections of the pelvis of the kidney are usually *unilateral,* whereas, the hematogenous forms are often *bilateral.* Fortunately, the majority of cases of pyelitis are due to ascending infection.

Pyelitis may occur at any *age;* it is not at all infrequent in *infants,* and every general practitioner, and especially every pediatrician, should be on the watch for it. *Girls* are attacked more often than boys.

Symptoms.—Pyelitis may be *acute* or *chronic;* and it may be *non-suppurative* or *suppurative.* In the latter case empyema of the renal pelvis, or *pyonephrosis,* may develop, especially when there is obstruction to the outflow through the ureter.

An ascending infection may pass beyond the pelvis of the kidney and cause *pyelonephritis,* or *surgical kidney.*

The symptoms may be very vague at the beginning, though in some cases there is *pain* or *sensitiveness* in the region of the kidney, which calls attention to the local site of the inflammation. In the mild cases there may be only a little *fever,* or none at all. In severe cases *fever, chills* and *sweats* may be present. Here again the routine examination of the *urine* is a great help in preventing one from overlooking the disease. There is albuminuria and pyuria. The reaction of the urine is acid in infections with Bacillus coli and Bacillus typhosus. Frequent micturition is a common symptom. In acute pyelitis there may be oliguria; in chronic pyelitis there is usually polyuria, except in acute exacerbations.

The existence of a *pyuria* or of a *hematuria* demands a thorough investigation until the source of the pus or of the blood has been determined.

Formerly much attention was paid to the presence of epithelial cells supposed to come from the pelvis of the kidney. Now we know that similar cells may have their origin in the bladder and ureter, and it is not worth while to spend time on trying to recognize cells of pelvic origin.

When pain is present it may be exaggerated by *palpation* of the kidney on the affected side. If there be a complicating hydronephrosis, pyonephrosis or pyelonephritis there may be local swelling, palpable, and demonstrable by the x-ray.

Diagnosis.—Let me emphasize by repetition—*as soon as pus or blood is found in the urine the condition should be thoroughly investigated until the source is definitely determined.* This may require resort to a cystoscopic examination and to ureteral catheterization. By use of these

modern methods the urologist can bring great aid to the general practitioner in differential diagnosis.

The keen general practitioner, however, will recognize the cases in

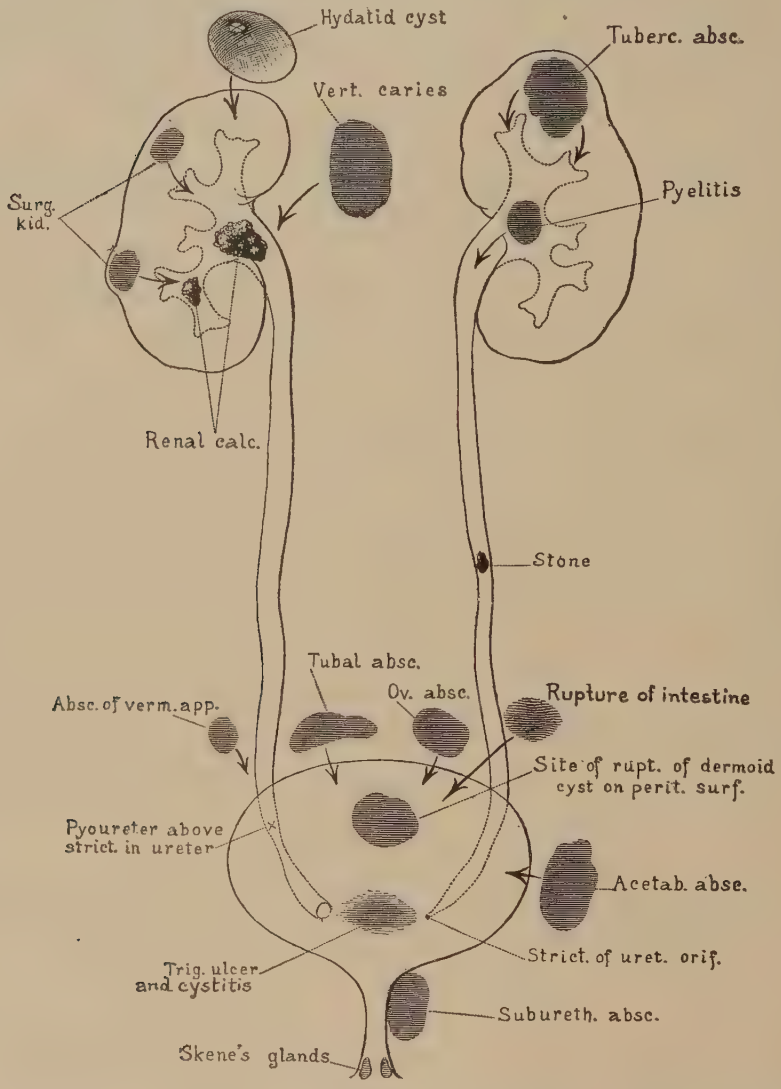

Fig. 480.—Diagram Showing Various Sources of Pus in the Urine. (After H. A. Kelly and C. F. Burnam.)

which such an investigation is necessary. The occurrence of pain in one flank, along with a history of slight febrile disturbance, or of sweats and chills, with digestive disturbance, will make him always think of pyelitis

or of pyelonephritis, and lead him at once to examine the urine. If a pyuria be found, the three-glass-test will be applied to make sure that the pus is mixed with the urine in the bladder. If this be positive, and the practitioner be untrained in special urology, a urological specialist may be invited thoroughly to irrigate the bladder and to undertake cystoscopy. Sometimes mere observation of the ureteral orifices will show that turbid urine is coming from one of the ureters, and not from the other. In most cases, however, ureteral catheterization, taking precaution not to infect a healthy ureter, will be desirable; a comparison of the urines of the two sides can then be made. The injection of a little sterile fluid into the pelvis of one kidney may call forth pain that the patient recognizes as precisely similar to the spontaneous pain experienced. A stricture of the ureter is sometimes found to be present on one side.

Microscopic examination of stained smears and cultures from the urine on each side will usually determine the etiological factor. If no bacteria grow in the cultures, under either aerobic or anaerobic conditions, tubercle bacilli should be sought for in especially stained smears of the sediment, and an animal should be inoculated with some of the sediment from the urine of each side.

Functional renal tests will determine (1) in how far the kidney on the affected side has been involved, and (2) the integrity of the other kidney. These tests are especially important if surgical interference be contemplated.

In the **differential diagnosis** we must distinguish pyelitis and pyelonephritis (1) from *nephrolithiasis;* and (2) from *perinephric abscess.*

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(*b*) *Hydronephrosis*

Definition.—A dilatation of the renal pelvis and its calyces, due to obstruction to the outflow of urine and the accumulation of non-purulent fluid, leading to pressure, pain and atrophy of the substance of the kidney.

Etiology.—Congenital hydronephrosis is known, due to abnormality of development of the urethra or of the ureter. In later life the two com-

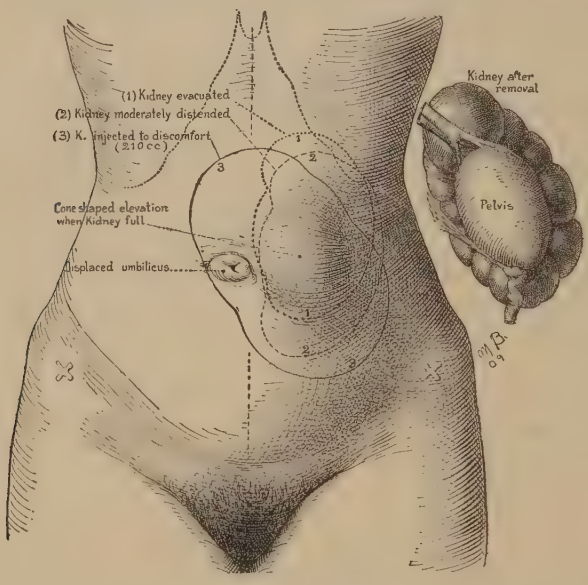

Fig. 481.—Position and Shape of Hydronephrotic Kidney in Various States of Distention. The Small Diagram to the Right Pictures the Kidney After Its Removal. The Cone-shaped Elevation with Fully Distended Kidney Was the Pelvis renalis. Note the Pushing of the Umbilicus to the Opposite Side of the Body. Deardorf, Ch. Home and Inf., May 10, 1907, patient of Dr. G. L. Hunner. (After H. A. Kelly and C. F. Burnam.)

monest causes of unilateral hydronephrosis are (1) stricture of the ureter following ulcer, and (2) the lodgment of a calculus in the ureter. Other causes include, (1) neoplasm pressing upon the ureter, and (2) tuberculous ureteritis. Bilateral hydronephrosis may be due to urethral stricture, to hypertrophy of the prostate, to cancer of the bladder, or to tabetic disturbances of micturition with retention.

An intermittent hydronephrosis sometimes manifests itself in association with Dietl's crises (*q. v.*).

Symptoms.—Hydronephrosis may cause no symptoms except the swelling. In later stages, symptoms resulting from compression, on the one hand, or from atrophy of the kidney with renal insufficiency, on the other, are likely to develop.

Diagnosis.—When the sac is large, it can be palpated in the region of the kidney, and, if there be doubt as to its nature, an aspirating needle may

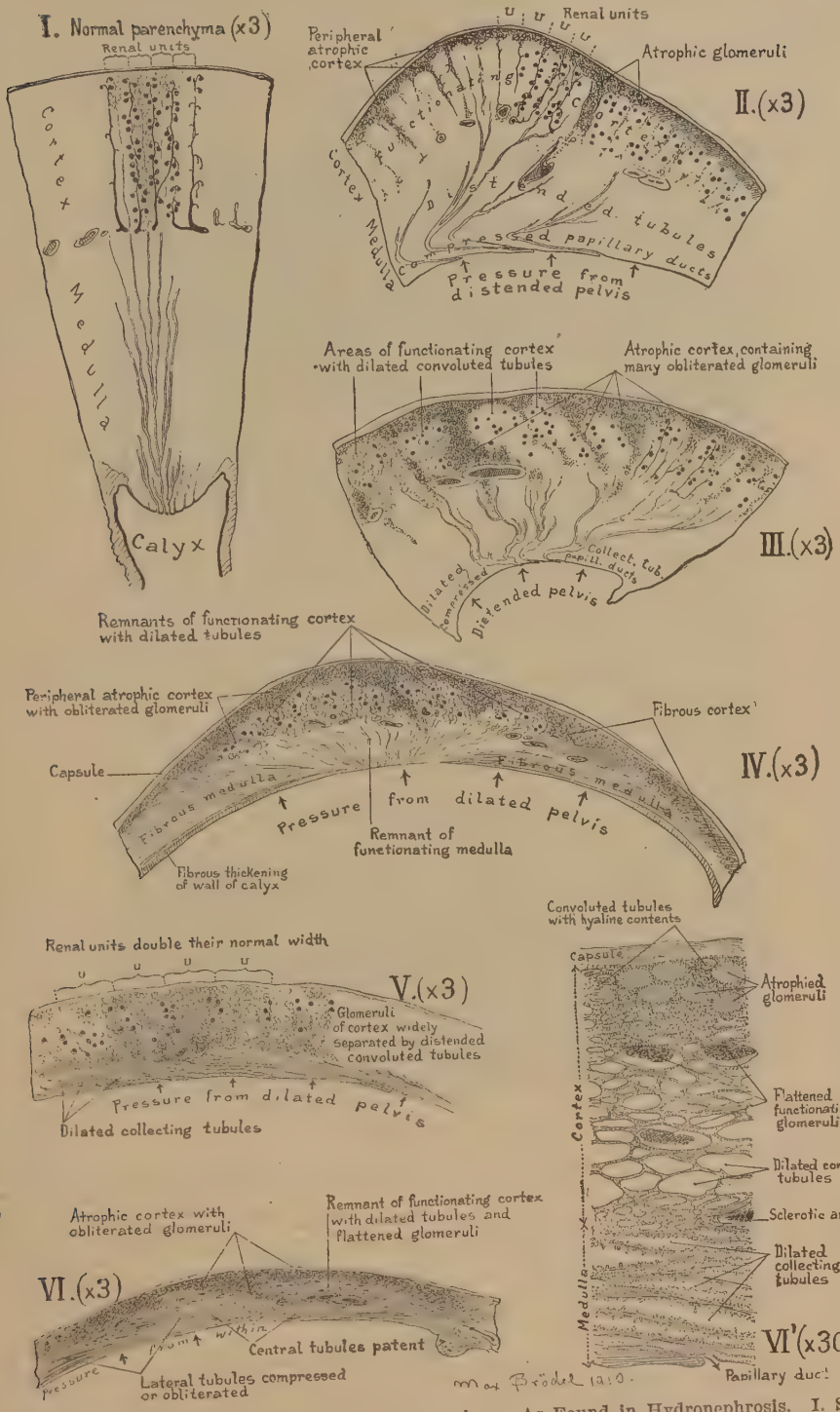

Fig. 482.—Progressive Changes in Renal Parenchyma As Found in Hydronephrosis. I. Shows Normal Parenchyma. The Succeeding Figures Show the Progressive Changes, up to VI, an Advanced Stage. VI' Is a Higher Magnification of VI. (After H. A. Kelly and C. F. Burnam.)

be introduced and the character of the fluid studied. Röntgenography and ureteral catheterization are important as diagnostic aids.

In the *differential diagnosis* we must distinguish hydronephrosis (1)

Fig. 483.—Moderate Grade of Hydronephrosis, Due to Stone in Lower End of Ureter. Pelvis Injected With Fifteen per cent Neutral Thorium Solution. Dilatation of Pelvis with Blunting of the Calyces and also Dilatation of Ureter. (Courtesy of Dr. J. E. Burns.)

from *pyonephrosis;* (2) from *ovarian cyst;* (3) from *sarcoma* of the kidney or of the retroperitoneal glands; and (4) from *congenital cystic kidney.*

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(c) *Nephrolithiasis*

(Renal Calculus, Stone in the Renal Pelvis)

Definition.—The formation in the pelvis of the kidney, or in the kidney itself, of calculi, through the deposition of solid constituents from the urine, usually deposited upon some organic nucleus.

Etiology and Pathogenesis.—Many studies have been undertaken to determine the cause of stone formation in the pelvis of the kidney, but the exact pathogenesis is still far from clear. The existence of many of the urinary solids in saturated solution owing to the colloidal state, the influence of local irritations, and the presence of foreign bodies, such as bacteria or degenerated epithelial elements, are believed to be important.

The concretions may vary in *size* all the way from small, gritty particles (*renal sand*), to very large calculi filling up the whole pelvis of the kidney and branching so as to occupy also the calyces, thus forming casts of the renal pelvis and its subdivisions.

The *chemical constitution* of renal calculi is described in Part IX. The stones may consist of (1) uric acid and urates, (2) oxalate of lime, (3) phosphates, or (4) of rarer constituents of the urine like cystin and xanthin. Stones consisting of carbonate of lime also occur.

In new-born children, uric-acid deposits are met with sometimes at the apices of the pyramids—the so-called *uric-acid infarcts* (a bad name).

Symptoms.—Some patients carry a stone in the pelvis of the kidney for years, or pass from time to time particles of urinary gravel, without ever suffering from an attack of renal colic. Most patients, however, have recurring attacks of outspoken *renal colic,* in which the pain may be atrocious, and between attacks there is, as a rule, more or less *pain,* or *aching,* on the affected side. Sometimes the pain is on the side *opposite* to that of the calculus, a fact that should never be forgotten, especially if surgical measures are to be undertaken.

The *symptoms of renal colic* are very characteristic. The onset of pain is abrupt. It begins in the flank on the affected side and radiates down

the ureter into the testicle and along the medial side of the thigh. Sometimes it passes upward into the back or forward to the abdomen and the chest. When the pain is severe it is usually accompanied by nausea, vomiting, and symptoms of collapse. Not infrequently an attack is ushered in with high fever and with sweating.

Sir William Osler, who has suffered from renal colic himself, describes three sorts of pain in an attack: "(a) a constant localized, dull pain, the area of which could be covered on the skin of the back in the renal region by a penny piece, and which could be imitated exactly by deep firm pressure on a superficial bone. (b) Paroxysms of pain radiating in the course of the ureter or into the flank, and as they increase accompanied by sweating, fainting and nausea. (c) Flushes or rushes of hot pain at intervals, often momentary, usually passing to the back, less often toward the groin. Dozens of these flushes relieve the monotony of (b). The symptoms persist for a variable period. In short attacks, they do not last longer than an hour; in other instances, they continue for a day or more, with temporary relief."

Fig. 484.—The Shaded Area Shows the Distribution of the Cutaneous Hyperalgesia After an Attack of Renal Colic. The Band Traverses Portions of the Fields of Distribution of the Eleventh and Twelfth Thoracic Nerves and of the First Lumbar. The Tunica vaginalis and the Lower Portion of the Left Abdominal Muscles Were Also Hyperalgesic. (After J. Mackenzie, "Symptoms and Their Interpretation," published by Shaw & Son, London.)

Between attacks of renal colic there is dull pain in the back, and occasionally hematuria. Attacks of "renal intermittent fever," probably due to pyelitis, may occur, similar to the "intermittent hepatic fever" of cholelithiasis. More or less pyuria is usually demonstrable.

Diagnosis.—When symptoms suggestive of renal colic, or of stone in the kidney without renal colic, are complained of, *röntgenography* should at once be undertaken. Formerly it was not always reliable, but it is rare now that a stone will be missed if a skillful röntgenologist give the matter his special attention. A röntgenogram should be made on the side on which the pain is experienced; but should no stone be found on this side, a röntgenogram of the other side should be made, since a number of cases have been reported in which the pain was on the side opposite the stone. It should be remembered, too, that a patient may have renal calculi on both sides. Great care should be exercised in reading röntgenograms of stones, especially when the stone is on the right side (renal stone; gall-stone; phlebolith).

In the *differential diagnosis* we must distinguish renal colic (1) from *intestinal colic;* (2) from *biliary colic;* and (3) from *Dietl's crises.*

Renal calculus should also be distinguished (5) from *stone in the bladder* (alkaline urine, x-ray).

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7. The Parasitic Nephropathies

These are very rare conditions. In the tropics, *hematochyluria* is observed, due to the presence of *filaria* in the renal lymphatics or blood vessels. *Echinococcus cyst* may involve the kidney or the urinary passages, but is more common between the bladder and the rectum, a cyst in this situation sometimes breaking into the bladder, when hooklets or pieces of the cyst wall will pass in the urine. An enormous nematode worm, known as *Dicotophyme renale,* and formerly known as *Eustrongylus gigas,* has, occasionally, been met with in the renal region of man,

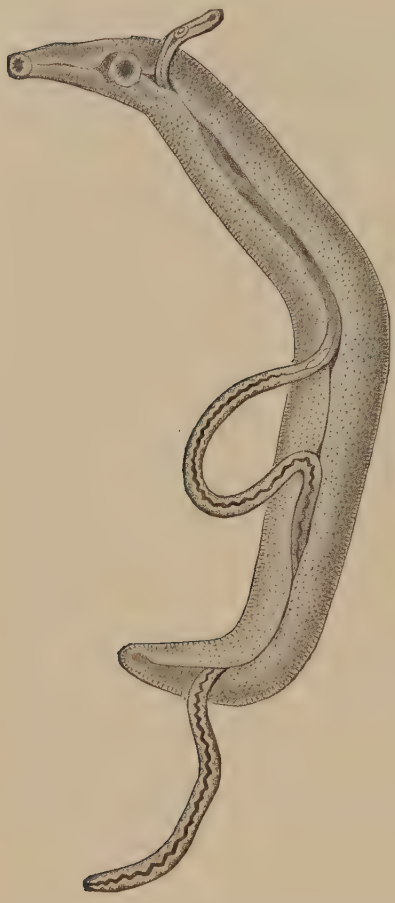

Fig. 485. — Schistosoma hematobium. (After A. Looss, in M. Braun's "Die thierischen Parasiten des Menschen," published by Bale Sons & Danielsson, London.)

where it may cause extensive destruction of the kidney. I have never seen a case, and it is certainly not common.

The ova of the African blood fluke (*Schistosoma hematobium*) and of the Asiatic blood fluke (*Schistosoma japonicum*) wander through the tissues and reach the wall of the bladder, rectum and vagina; they may occur in many organs including the kidneys. The irritation they cause gives rise to "bilharzian hematuria." The worms themselves live in the veins of the liver, intestine, bladder, etc.

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8. The Neoplastic Nephropathies

(Tumors of the Kidney)

These include (1) *hypernephroma;* (2) *carcinoma;* (3) *sarcoma;* (4) *teratoma;* (5) *malignant papillary cystadenoma;* and (6) certain *benign tumors* of the kidney (adenoma, lipoma, fibroma, angioma, myxoma). Only the more important of these will be described here.

(*a*) *Hypernephroma of the Kidney*

Definition.—A tumor, arising in the kidney substance, probably from some embryonic residue there, either (1) aberrant suprarenal glandular tissue, or the so-called "adrenal rests" of Grawitz, or (2) remains of the wolffian body or primitive renal blastema.

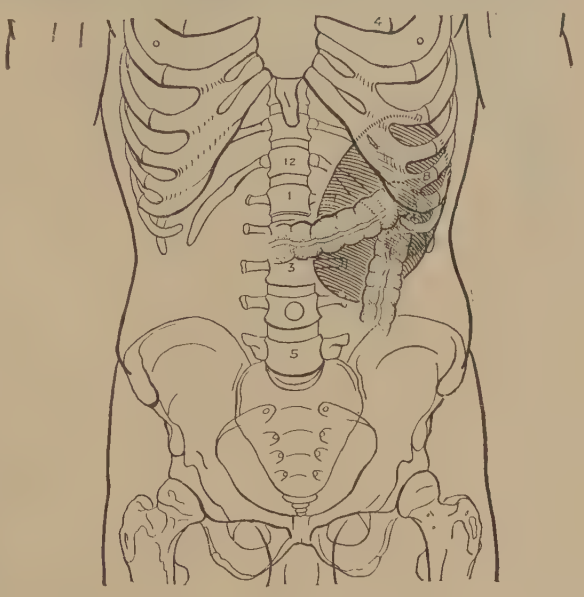

Fig. 486.—Diagram of Adrenal Tumor with Displacement of the Left Kidney Downward and Lateralward. Note that the Mass Lies Behind the Colon.

Site.—A *hypernephroma* most often has its origin at the upper extremity of the kidney, just beneath the capsule.

Size and Consistence.—The tumor may vary in size from that of a pea to that of a child's head, or be even larger. The small tumors are firm, but the large ones are soft, and often contain blood cysts or areas of necrosis.

Histological Appearance. — The constituent cells of a hypernephroma closely resemble those met with in the suprarenal cortex. An alveolar arrangement is often met with. The cells contain glycogen and lecithin, as well as fat. The growth of the tumor causes a pressure-atrophy of the substance of the kidney. The tumor often grows into the renal veins and extends along these veins for a considerable distance. In one of H. H. Young's cases, it had grown into the vena cava and extended upward beyond the diaphragm, and downward as far as the brim of the pelvis. In one case in the bibliography, the venous invasion extended as far as the atrium of the heart. Fragments of such ingrowths may break off and be carried by the blood current to remote parts of the body. Metastases may be found in any of the organs and they are often found in the bones.

Symptoms.—In small tumors and in slow growing tumors there may be no symptoms, but when the tumor is large or the growth rapid, the symptoms are usually pronounced, and consist of (1) *hematuria,* (2) *pain,* and (3) *palpable tumor.*

Hematuria may be the sole symptom. Israel reports a case in which there was hematuria for twelve years.

The *pain* may be a dull ache in the lumbar region or it may radiate along the nerves.

A *palpable tumor* in the flank is an important diagnostic sign, often the first sign of hypernephroma. It is found, as a rule, in the lumbar

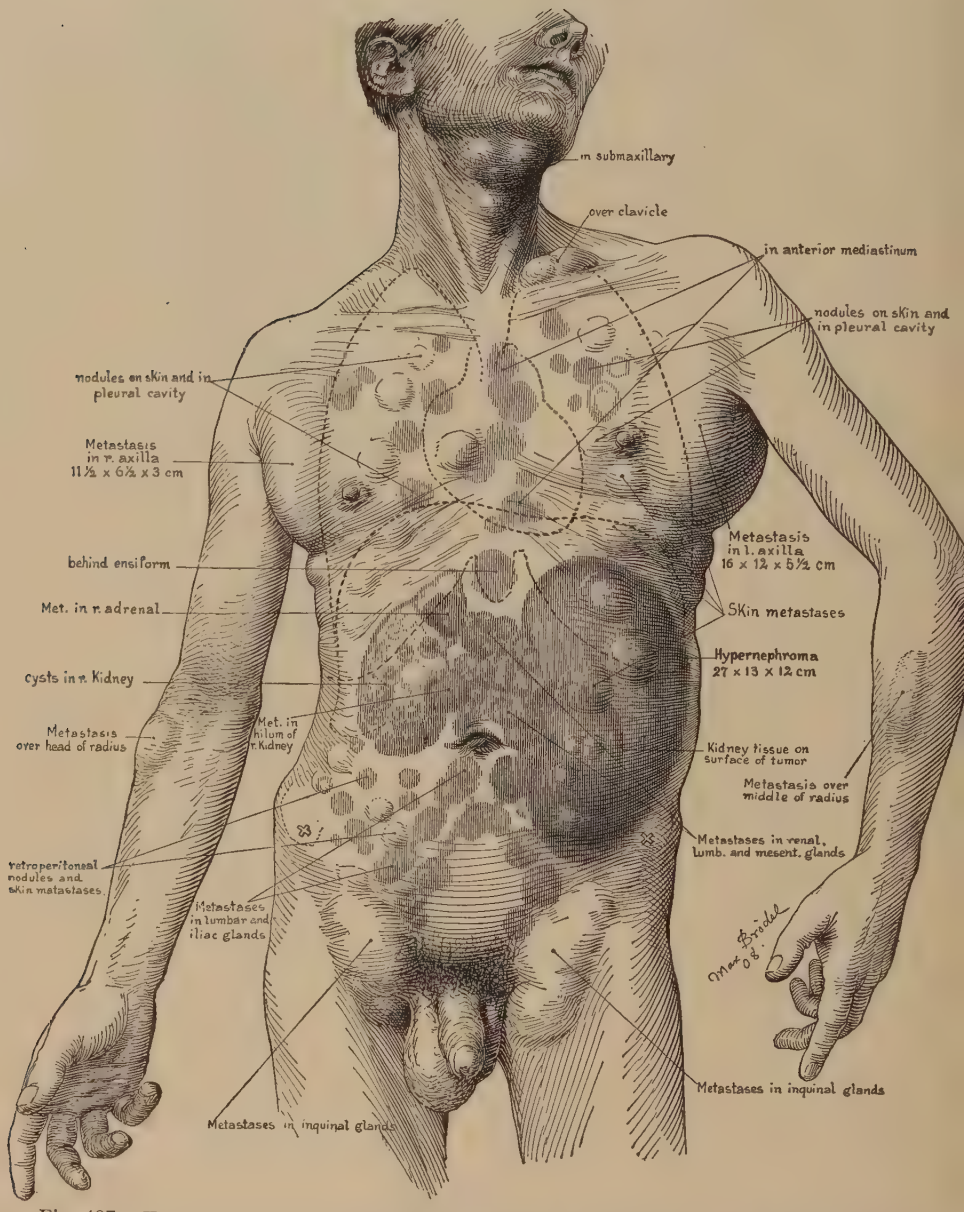
r. submaxillary
over clavicle
in anterior mediastinum
nodules on skin and in pleural cavity
nodules on skin and in pleural cavity
Metastasis in r. axilla 11½ x 6½ x 3 cm
behind ensiform
Met. in r. adrenal
cysts in r. Kidney
Metastasis over head of radius
Met. in hilum of r. Kidney
retroperitoneal nodules and skin metastases
Metastases in lumbar and iliac glands
Metastasis in l. axilla 16 x 12 x 5½ cm
Skin metastases
Hypernephroma 27 x 13 x 12 cm
Kidney tissue on surface of tumor
Metastasis over middle of radius
Metastases in renal, lumb. and mesent. glands
Metastases in inguinal glands
Metastases in inguinal glands

Fig. 487.—Hypernephroma and Metastases. Malignant Hypernephroma; the Tumor Originated in the Left Kidney and Metastasized As Indicated in the Drawing, the First Evidence of Trouble Being a Swelling in the Left Axilla. The Kidney at that Time Was Just Palpable; Death Occurred Within Six Weeks, When the Development of the Growth and Its Metastases Had Reached the Enormous Extent Shown in the Picture. The Subject in the Case Was Insane. (After H. A. Kelly and C. F. Burnam.)

region, extending forward into the abdominal cavity. It lies between the ribs and the iliac crest, and usually there is no space between the tumor and the lumbar muscles. It is behind, and lateral from, the colon.

Varicocele, on the right side, may be due to pressure of the growth. When the vena cava is invaded signs of *venous obstruction* appear.

Diagnosis.—Hematuria is the symptom that usually brings the patient to the physician, and the previously unsuspected tumor is found on palpation. Pain is of but little help as a diagnostic sign.

In the *differential diagnosis* we must distinguish hypernephroma (1) from *renal tuberculosis* (pyuria, tubercle bacilli in sediment); (2) from *nephrolithiasis* (renal colic, absence of tumor as a rule, röntgenogram); (3) from *hydronephrosis* and *pyonephrosis;* (4) from *essential hematuria,* and *other forms of hematuria;* (5) from *other tumors of the abdomen;* and (6) from *other renal tumors* (carcinoma, sarcoma, malignant adenoma, benign tumors).

Fig. 488.—Large Tumor of the Kidney in a Child. The Tumor Mass Is Outlined in Black. The Tumor Was Probably a Sarcoma, Though the Proof of This Is Lacking. (After W. Osler.)

(*b*) *Carcinoma of the Kidney*

This is an exceedingly rare disease; most of the cases formerly reported were probably hypernephromas. True primary adenocarcinoma does occur, and one has been reported by T. S. Cullen. The condition is so rare, however, that it need not be considered here.

Metastatic carcinoma of the kidney is occasionally met with, though the kidneys are not a favorite site for carcinoma metastases.

(*c*) *Sarcoma of the Kidney*

This rare tumor is sometimes met with in children, and may be of the round-celled, or of the spindle-celled, variety. The symptoms and signs are much like

those of hypernephroma, though the course is much more rapid. It is probably impossible to distinguish sarcoma from hypernephroma before nephrectomy.

(d) *Teratoma of the Kidney*

Occurrence.—Remarkable tumors of the kidney have been described that, in my opinion, should come under the designation of *teratoma.* In the bibliography they are reported as *dermoid cysts,* as *rhabdomyoma,* and as *mixed tumors* of the kidney. They are most often observed in children.

Symptoms.—A palpable tumor is the first thing noticed.. It usually grows rapidly and may attain to a large size. Hematuria and pain are less common than with other renal tumors. Death occurs within a year.

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B. Special Diagnosis of the More Important Diseases of the Urinary Passages

1. Diseases of the Bladder

(*a*) *Inflammation of the Bladder* (*Cystitis*)

Etiology.—Any *obstruction to micturition* (*e. g.*, urethritis, urethral stricture, enlarged prostate, weakness of bladder wall) or any *foreign body* in the bladder (calculus, tumor), predisposes. The *exciting cause* is always a bacterial infection: (1) most often through the urethra, (a) by direct extension (gonorrhea) or (b) by introduction of instruments (catheter, sound); (2) sometimes from above from a nephritis or a pyelitis of hematogenous origin). Some bacteria (*Bacillus coli, gonococcus*) do not cause ammoniacal fermentation; others do (*e. g., Bacillus proteus*).

A cystitis may be a simple catarrh, or it may be purulent or pseudomembranous. It may be acute or chronic (recurrent). Tuberculous cystitis with ulceration is not rare (see below).

Symptoms.—*Fever;* often *chill;* vesical *tenesmus;* painful and frequent *micturition. Urine:* Cloudy; contains much mucus and abundant white sediment (pus, epithelium); the amount of albumin corresponds to the amount of pus present; reaction usually acid at first, except in infection by catheter and in paralysis of bladder, then alkaline with ammoniacal fermentation (triple phosphates and ammonium urate crystals in sediment, foul odor). On *cystoscopy* areas of hyperemia, and sometimes ulceration, may be visible.

(*b*) *Tuberculosis of the Bladder* (*Cystitis tuberculosa*)

This is usually due to descending infection (from hematogenous renal tuberculosis); rarely, secondary to genital tuberculosis (especially to hematogenous prostatic tuberculosis). The symptoms are those of cystitis. Tubercle bacilli are demonstrable in the urine. Cystoscopic examination permits of an exact localizing diagnosis. A thickened ureter may be palpable through the rectum or the vagina.

(*c*) *Stone in the Urinary Bladder* (*Vesical Calculus*)

Occurrence.—*Primary stones* arise through crystallization from urine that has not undergone decomposition; they consist usually of urates or of oxalates, rarely of cystin, xanthin or carbonates.

Secondary stones may arise in the decomposing urine of an infectious cystitis; they include the phosphate stones.

Symptoms.—In *non-infected cases:* (1) irregular disturbances of micturition due to variable position of the stone; (2) vesical tenesmus; (3) hematuria (much less blood than in neoplasms). The stones may be bimanually palpable (one hand on the abdomen, the other in the rectum or vagina).

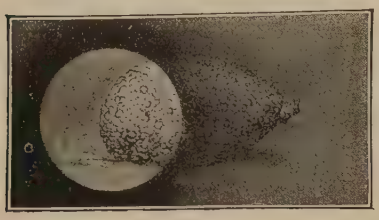

Fig. 489.—Open-air Speculum View of Stone. (After H. A. Kelly and C. F. Bufnam.)

In *infected cases,* the tenesmus is greater, and pyuria exists.

The passage of a sound, cystoscopy, and röntgenography make the diagnosis certain. In making a röntgenogram, the patient should be undressed; for a case is known in which a bladder was opened owing to a shadow in the X-ray plate due to a trouser button!

Differential Diagnosis.—We must distinguish stone in the bladder: (1) from *tumor of the bladder* (cystoscopy); (2) from *renal calculus* (cystoscopy and röntgenography of both renal and vesical areas); (3) from *chronic cystitis;* and (4) from *tuberculosis of the bladder.*

Fig. 490.—X-ray of a Large Egg-shaped Vesical Calculus. Note the Homogeneous Smooth, Well-defined Shadow Cast by the Stone. At Times Concentric Rings May Be Detected in the Skiagram. (After S. G. Scott, "Arch. of the Röntgen Ray," published by Rebman & Co., London.)

(*d*) *Tumor of the Urinary Bladder* (*Papilloma; Cancer*)

Like renal tumors, tumor in the bladder is often announced by *hematuria* and by *severe anemia* before other signs appear (tenesmus, radiating pains, tumor-fragments in the urine).

For the diagnosis, bimanual palpation, sounding, cystoscopy, etc., are helpful. A tumor here may be benign (*papilloma*), or malignant (*carcinoma*).

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C. Special Diagnosis of the More Important Diseases of the Male Genital Organs

1. Diseases of the Prostate

(*a*) *Inflammation of the Prostate* (*Prostatitis*)

This may be *acute, subacute* or *chronic.*

i. Acute Prostatitis

The patient has fever and complains of pain on sitting and on defecation (rectal tenesmus); there is vesical tenesmus with blood at the end of micturition; occasionally retention of urine occurs.

The inflammation may become suppurative (*prostatic abscess*); if so, on rectal palpation, a soft, elastic swelling in one lobe can be felt, over which the rectal mucosa feels thickened and velvety; on passing a Nélaton catheter into the urethra an obstruction is met in the prostatic region. Such abscesses are usually due either to the gonococcus or to the tubercle bacillus; rarely, to other bacteria (Bacillus coli, staphylococci). Spontaneous rupture of the abscess into the rectum or the bladder is common.

ii. Chronic Prostatitis

Symptoms.—The prostate is enlarged and tender. The patient has a feeling of pressure in the rectum. Prostatorrhea may occur during and after defecation. Sometimes there is lessened potentia and marked mental depression.

The disease is much more common than is generally realized, though the excessive zeal of some urogenital specialists must be discounted.

T. McCrae and H. H. Young have called attention to the referred pains and other remote effects of chronic prostatitis. Four distinct groups of referred pains are described: (1) those involving the rectum, perineum and urethra; (2) those involving the groin and scrotum; (3) those extending along the N. ischiadicus to the buttocks, hips, thighs and legs; and (4) those extending into the back and the region of the kidneys, sometimes closely simulating an attack of renal colic. (See Head's zones of referred pains.)

Severe neurasthenic states, and functional disturbances of cardiac rhythm are sometimes due to chronic prostatitis. Chronic infections of the prostate may also be responsible for metastatic chronic arthritis or for chronic myocarditis.

Diagnosis.—A careful examination of the prostate should be made as a part of the routine in general clinical examinations of the adult male (See Methods of Examination of the Prostate). The enlargement, the

nodules and patchy indurations, the tenderness, the involvement of neighboring structures with fixation, leave no doubt as to diagnosis when they are present. Should the prostate feel normal, notwithstanding the existence of suspicious symptoms, the *succus prostaticus* should be stripped out and examined microscopically (*q. v.*).

The referred pains are due to irritation of the nerve filaments in the interacinous inflammation. The sexual symptoms depend partly upon pathological changes in the verumontanum and in the ejaculatory ducts. Fine comma threads from the prostatic ducts may be present in the urine, in the third glass of the three-glass-test.

In 358 cases analyzed by Young, the following incidence of symptoms was found: *frequent urination* in 90; *painful urination* in 46; *urgency of urination* in 25; *difficulty in urination* in 11; *irritability of deep urethra* in 11; *pain* at end of urination in 7, at the beginning of urination in 3; definite *obstruction* in 34. As to the *referred pains* observed, they were in the *lumbar* region in 64, in the *renal* region in 8; they simulated *renal colic* in 10; they were in the *perineum* in 35, *suprapubic* in 22, in the *groin* in 18, in the *urethra* in 14, in the *rectum* in 13, in the *thighs* in 12, in the *hips* in 10, and along the *sciatic* in 5.

In the *differential diagnosis* we have to distinguish ordinary chronic prostatitis: (1) from *hypertrophy* of the prostate; (2) from *tuberculosis* of the prostate; (3) from *cancer* of the prostate; and (4) from *other diseases,* suggested by the referred pains, the neurasthenic states, or the circulatory disturbances.

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(*b*) *Hypertrophy of the Prostate*

Definition.—An enlargement of the prostate, due most often to hypertrophy of the glandular tissue, sometimes to enlargement of the fibrous and muscular elements, occurring usually in advanced life and often leading to obstruction to urination and "residual urine."

Symptoms.—An elderly man begins to have difficulty in emptying his bladder (hesitation, straining, small stream, increased frequency), which gradually increases in degree. After a while there is complete retention, and a "catheter life" or operation becomes necessary. Enlargement is palpable per rectum, except when the middle lobe is alone involved; the latter is visible on cystoscopy. Sometimes there is a sudden inability to void after a shorter or longer period of nycturia, pollakiuria, and small urinary stream. Occasionally there is hematuria. It should not be forgotten that the first time a catheter is passed complete retention may follow, and render a catheter life or operation necessary.

Differential Diagnosis.—We must distinguish hypertrophy of the prostate (1) from *beginning tabes* (in which there is also often frequent urination, residual urine, and trabeculated bladder; the tabes will not be easily overlooked if it be thought of, or if actual incontinence exists. The relative youth of the patient, the absent knee kicks, the Argyll-Robertson pupils, the lightning pains, and an examination of the cerebrospinal fluid when there is any doubt will help to differentiate); (2) from *stricture of the urethra*, (which may cause symptoms suggestive of obstruction due to enlarged prostate); and (3) from *malignant disease of the prostate* (*q. v.*).

Complications.—(1) Infection of the bladder (examination of the urine); (2) inability to empty the bladder completely ("residual" urine, determined by catheterization immediately after voiding spontaneously); (3) pyelitis (unilateral or bilateral lumbar pain, persistent digestive disturbances, and, especially, acute attacks of retention, with fever, chill, vomiting, diarrhea, headache and sometimes mild delirium).

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(*c*) *Tumors of the Prostate* (*Carcinoma; Sarcoma*)

Symptoms.—The disease rarely occurs before the age of 50. Half the patients are over 60. The symptoms may closely resemble those of simple hypertrophy. It should be remembered that in enlargement of the prostate, that due to cancer and that due to simple hypertrophy stand in the ratio of 1:4. Pain and hematuria are commoner in cancer than in hypertrophy.

Diagnosis.—On rectal palpation, a nodular, asymmetrical growth in the prostatic region, or a firm mass, not especially tender on pressure, and sharply limited lateralward, is suggestive of malignant disease. A *stony hardness* is an important diagnostic sign. On cystoscopic examination, instead of two smooth projections, a nodular, irregular mass may be visible. A complaint of sciatica, or the finding of metastases, especially in bones, may confirm the diagnosis. Carcinomata are firm and nodular; sarcomata are softer and more rounded. In suspicious cases exploratory prostatectomy should be undertaken early. In advanced cases it is useless.

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2. Diseases of the Testicle, Epididymis, and Funiculus spermaticus

(*a*) *Inflammation of the Testicle* (*Orchitis*)

Occurrence.—The disease is less common than involvement of the epididymis, and occasionally it is secondary to the latter by extension through the lymph channels; more often it is metastatic in origin, as in mumps (*orchitis parotidea*), in small-pox (*orchitis variolosa*), in sepsis, in pneumonia, and in meningitis. A chronic orchitis may lead to atrophy and to fibrosis testis. Tuberculosis and lues may involve the testicle.

Symptoms.—When acute, there is sudden painful swelling involving the testicle itself. If abscess be suspected, exploratory puncture may become necessary. (Caution! The patient should be warned beforehand that, whether punctured or not, complete atrophy of the testicle, as a sequel of the orchitis, is a possibility.)

Tuberculosis of the testicle and lues cause chronic enlargements.

(*b*) *Tumors of the Testicle*

Primary sarcoma occurs in children, and in men under forty. It is common in instances of undescended testicle, especially after trauma. *Cancer* and *teratoma* are rare. Such tumors appear as solid masses in the testicle and cause neuralgic pains in the spermatic cord.

(*c*) *Inflammations of the Epididymis* (*Epididymitis*)

Occurrence.—Usually, the disease arises by propagation from the urinary passages (urethritis, prostatitis); rarely, it is metastatic or traumatic in origin. The most common form is that due to the *Gonococcus* (*epididymitis gonorrhoica*), usually accompanied by a periorchitis, and often

suppurative, though even then subsiding usually spontaneously. Epididymitis is not uncommon as a complication of cystitis due to catheterization, bladder paralysis, or hypertrophied prostate (*Bacillus coli, Staphylococcus*). As a sequel, chronic obstruction of the seminal duct often results; if bilateral, this causes permanent *sterility*, due to azoöspermia.

Symptoms.—The two prominent symptoms are (1) fever and (2) painful swelling of the epididymis.

Diagnosis.—Local findings; anamnesis; demonstration of primary infection. Genital tuberculosis should be kept in mind in the differential diagnosis.

(*d*) *Hydrocele Testis*

This has been described under Methods of Examination (*q. v.*).

(*e*) *Varicocele*

By this is meant an abnormal dilatation and tortuosity of the veins of the spermatic cord; on palpation, the veins feel like a snarl of fishworms.

It is common in young men, owing to increased vascularity at this age, and to obstruction to venous outflow. The condition is more common on the left than on the right side. Varicocele has no deleterious effect upon the testicular function.

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3. Gonorrhea in the Male, and its Complications

Etiology.—The *gonococcus* of Neisser, a biscuit-shaped diplococcus, staining easily with methylene blue, free and inside of pus cells (important for diagnosis). Incubation period: 1-3 days.

Symptoms.—The disease begins with a tickling and burning sensation at the meatus, with redness, swelling and stickiness there, soon followed by pain on micturition and a mucous discharge (containing gonococci), which in three or four days becomes more abundant, changing to creamy pus (*urethritis acuta purulenta*). Flocculi and shreds are present in the urine. Painful nocturnal erections may be a distressing symptom. Untreated, the discharge may grow thinner and scantier in three or four weeks. If the posterior urethra become involved (*urethritis posterior*) there is pain in the perineum, tenesmus, pollakiuria, and often blood at end of micturition (see three-glass-test). In chronic cases the discharge may become thin and less purulent (*gleet*).

Complications and Sequelae.—Epididymitis; prostatitis; spermatocystitis; Cowperitis; cystitis; chronic gonorrhea; urethral stricture; gonorrheal arthritis; gonorrheal endocarditis; condyloma acuminatum; sterility.

Diagnosis.—Anamneses; external inspection and palpation of the genitals (pus infiltrations, complications); microscopic examination of smears (urethral pus, prostatic secretion); three-glass-test; palpation of the prostate, seminal vesicles and epididymis; examination of the heart and of the joints.

In *chronic cases* the urethral sound may aid; occasionally endoscopy and bacteriological examination of the expressed prostatic secretion will be necessary.

To decide whether *marriage* is permissible, we examine (1) smears of the urethral secretion, especially 24 hours after provocatory irritation with urethral sound or with argentamin solution (1:3000 in anterior urethra three times the day before for five minutes at a time); and (2) the expressed prostatic secretion. We also determine presence of motile spermatozoa in the sperm. The patient should be treated (1) until there are no longer any urethral shreds composed chiefly of pus cells, and until (2) the gonococcus complement-fixation-test is permanently negative.

Fig. 491.—March of the Gonococcus in the Male. (After R. Guiteras.)

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D. Special Diagnosis of Certain Important Diseases of the Female Genital Organs

The diseases of the genital organs in the female belong to the special domain of gynecology. Here we shall refer only to certain conditions especially important for the general practitioner and the internist in their work. For a full discussion of these topics text-books of gynecology should be consulted.

1. Gonorrhea in the Female, and its Complications

Occurrence.—The disease is often transmitted by apparently healthy men to their wives. In women, the disease may be acute or chronic. An acute stage may be absent altogether; in chronic infections, there may be acute exacerbations, simulating a fresh infection.

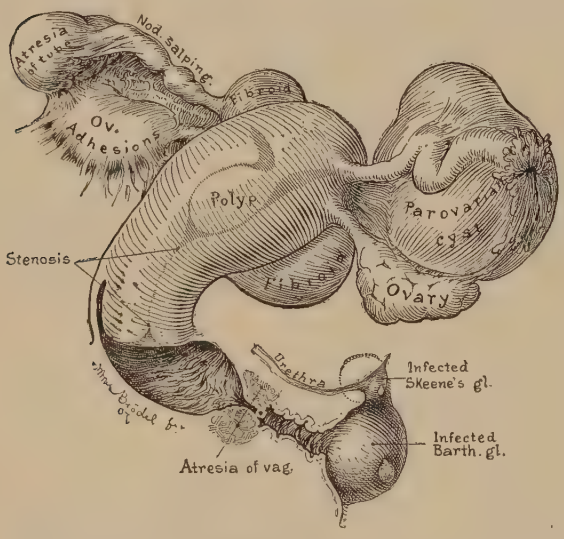

Fig. 492.—Some of the Causes of Sterility in the Female Brought Together in One Diagram. An Infection of Skene's Tubules or of Bartholin's Gland Significant of Gonorrhea; Atresia of the Vagina; Stenosis of the Cervix; a Polyp Hanging into the Uterine Cavity; Fibroid Tumors; a Fibroid at the Attachment of the Uterine Tube; a Parovarian Cyst Splinting the Tube and Separating It from the Ovary; a Nodular Salpingitis Due to Gonorrheal or Tubercular Inflammation; an Atresia of the Tube, of Inflammatory Origin; Ovarian and Tubal Adhesions. (After H. A. Kelly.)

Prostitutes are almost universally infected.

Localization. — Most often, the urethra, and its lacunae is the site; next, in frequency, the cervix uteri; less often, the vulva and vagina; occasionally, the endometrium and the uterine tubes (ascending gonorrhea), the ovaries and peritoneum (pelvic inflammatory disease; gonorrhea of adnexa). Rectal, oral, conjunctival endocardial or articular gonorrhea may occur.

Symptoms.—No symptoms at all may be noticed, or the symptoms may be very severe. When marked, there may be a burning sensation in the vagina and in the external genitals; pains on walking or on sitting; painful micturition; and an abundant, smarting, yellowish discharge. On examination of the severer cases, one sees redness and swelling of the vulva, tender introitus, condyloma acu-

minatum, and a reddened urethral meatus, whence a drop of pus can be expressed (*gonococci!*)

Bilateral infection of Bartholin's glands is common, with formation of retention-cysts or abscesses. In *gonorrheal pelvic inflammatory disease,* there are irregular menorrhagias, and periodic pains in the lower abdomen; the disease often leads to sterility and to chronic invalidism; bimanual palpation reveals inflammatory thickening, sometimes abscess (*pyosalpinx*).

The eyes of a baby may be infected during labor, if the mother has gonorrhea and *ophthalmia neonatorum* develop. As a routine, a drop of 1 per cent silver-nitrate solution should be placed in the eye of every new-born child. If this rule of Crédé's were followed a large proportion of blindness would be prevented.

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2. Diseases of the Uterus

(*a*) *Endometritis*

If we include under it all the conditions that have been so called, endometritis is the commonest disease of the female genitals.

Etiology.—I. *Infectious endometritis* may be due to (a) puerperal sepsis, or puerperal sapremia; (b) non-puerperal sepsis (gonorrhea); (c) diphtheria; or (d) tuberculosis.

II. *Chronic non-infectious endometritis* or *"physical" endometritis* (more often, as T. S. Cullen has shown, a *hyperplasia* than a true inflammation) may be due to (a) circulatory disturbances (displacements; congestions), (b) recurring catarrhal infections, (c) submucous myoma, (d) retentions after abortion or childbirth. There may be a marked tendency either to atrophy (*endometritis atrophicans*), or, more often, to hypertrophy of the mucosa (*endometritis hypertrophicans*). A peculiar form is the so-called "membranous dysmenorrhea" (*endometritis exfoliativa*). *Caution!* Do not confuse the discharge in membranous dysmenorrhea with the decidua of an abortion!

Symptoms.—The symptoms are similar in the different forms, and are often complicated by those of myometritis and of perimetritis.

In the *acute* forms, there are fever, chills, pain in the abdomen and back, and a uterine discharge; often, also, the patients suffer from constipation, meteorism, dysuria and nausea. Later on, the symptoms resemble those of the more chronic forms.

In the *chronic* forms, a persistent uterine discharge, a recurring menorrhagia, pain (spontaneous, and during coitus), and disturbed menstruation, are complained of. In addition, vesical, rectal, and general nervous symptoms may be present.

Diagnosis.—This depends upon (1) the anamnesis; (2) the above symptoms; and (3) an exact gynecological examination of the uterus, the adnexa, the bladder and the rectum.

The chief things that call attention to the endometrium are: (1) Excessive menstrual flow or intermenstrual hemorrhage; (2) supposed infection; (3) menstrual pain and (4) sterility.

The cervix of the uterus may be dilated and the cavum uteri curetted; the "uterine scrapings" should be fixed, sectioned, and examined microscopically to exclude carcinoma or sarcoma.

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(*b*) *Uterine Hemorrhage* (*Menorrhagia and Metrorrhagia*)

Definition.—Increased menstrual flow is known as *menorrhagia;* any uterine hemorrhage other than menstrual flow is known as *metrorrhagia.*

The source of a uterine hemorrhage should be carefully sought. Some of the commoner causes will here be tabulated.

i. Hemorrhages During Pregnancy, Parturition and the Puerperium

In *early pregnancy,* hemorrhage may be due to (1) threatened or beginning abortion (miscarriage), or (2) syphilis; in *later pregnancy,* to (1) placenta praevia, (2) varicose veins, (3) cervical polyp or erosion, or (4) carcinoma.

During *parturition,* hemorrhage may be due to (1) placenta praevia, (2) tear of the external os, or (3) premature separation of a normally situated placenta.

A *postpartum hemorrhage* may be due to (1) atony of the uterus, (2) trauma of the genital tract (cervix, vagina, vulva, perineum), (3) retained portions of placenta, or (4) placenta succenturiata.

In the puerperium, aside from early hemorrhage due to atony or retained placenta, there may be hemorrhage later from *delayed involution,* in which event, bimanual palpation reveals an organ too large, too soft, and too relaxed.

Of the *neoplasms* that may account for hemorrhage during pregnancy, labor, and the puerperal period, myoma and carcinoma may be mentioned.

In *ectopic* or *extrauterine pregnancy,* atypical uterine hemorrhage may occur. After missing one or two periods, irregular bleeding appears, or, with a large hemorrhage, a decidua is expelled. Examination reveals an enlarged and displaced uterus, an open cervix, and a soft, elastic, palpable mass to one side of, and behind, the uterus, and connected with it. Secretion can be expressed from the breast.

A *ruptured tubal pregnancy* yields signs suggesting internal hemorrhage and acute peritonitis, violent abdominal pain, vomiting, tachycardia, collapse and pallor (in the absence of fever).

ii. Hemorrhages Not Associated with Pregnancy or the Puerperium

Every patient complaining of atypical uterine hemorrhage should submit to a thorough gynecological examination. The hemorrhage may come, either from the uterus, or from a lower portion of the genital tract.

(a) *From the vulva or introitus* it may be due to (1) coitus (rape), or (2) trauma from falling on sharp object, etc.

(b) *From the vagina,* it may be due to (1) trauma, especially in elderly women (digital or specular examination, coitus), owing to adhesive colpitis senilis; (2) ulceration from pessary, or (3) carcinomatous ulcer.

(c) *From the cervix,* it may be due to (1) erosions; (2) beginning carcinoma of the portio vaginalis; (3) luetic ulcer; or (4) endocervical polyp, catarrh or cancer.

(d) *From the body of the uterus,* it may be (1) a *menorrhagia* (due to chlorosis; chronic passive congestion; diseased adnexa, including chronic oöphoritis, cystic ovaries, salpingitis, para- and peri-metritis; atonic uterus, displaced uterus, endometritis, neoplasm, including carcinoma, sarcoma, chorionepithelioma, and myoma or "fibroid" of the uterus, or (2) a *metrorrhagia* (due to one of many of the same causes, especially to myoma, carcinoma or endometritis hypertrophicans).

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(c) *Cancer of the Uterus (Carcinoma uteri)*

Occurrence and Symptoms.—The disease may occur at any age but it is commonest between 35 and 60; it is most frequent near the menopause. A thin, watery, irritating vaginal discharge with penetrating odor may be the first symptom. Menorrhagia or metrorrhagia is common. Pain may be entirely absent in the early stages; later, a persistent dull pain in the back is felt, or the patient may suffer from uterine cramps. In the later stages the emaciation and the cachexia become prominent.

Physical Examination.—In *cancer of the cervix*, the finger finds the

cervix enlarged and may bring away a little blood with it; a cauliflower growth, or an ulcer, may be felt, or later, the cervix may have disappeared and instead of it, a hole surrounded by firm puckered tissue will be felt. *Caution!* Do not confuse with (1) everted cervix, (2) superficial bleeding erosions (plâques), or (3) nabothian cysts.

In *cancer of the fundus,* the body of the uterus may vary in size from normal to that of a three months' pregnancy. The diagnosis will then depend, in the presence of suspicious symptoms, upon curettage and microscopic examination of the "scrapings."

Microscopic Examination.—If we suspect cancer of the cervix, a wedge of tissue may be excised and studied histologically; if cancer of the fundus be suspected, we examine the uterine scrapings. *Caution!* The pathologist making the histological examination should have had special training in the study of uterine scrapings. (T. S. Cullen.)

Fig. 493.—Illustrates the Three Principal Foci from Which Carcinoma of the Uterus Takes Its Origin. (After H. A. Kelly.)

Early Diagnosis.—The following are H. A. Kelly's rules: (1) The physician attending a woman at labor should, six or eight weeks later, make an examination and find out what lesions remain. (2) Every woman who has borne children should have a careful gynecological examination at least once every year until she is 55 years old.

An adoption of these rules would lead, in the majority of cases, to the discovery of cancer in its incipiency.

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(*d*) *Fibroid Tumor of the Uterus* (*Myoma uteri*)

Size and Site.—The tumors may vary in *size* from that of a small nodule to that of a mass weighing many pounds (in one case, 140 pounds).

The *site* of the tumor may be (1) subserous, (2) interstitial, or (3) submucous. The tumor always arises from the myometrium.

Symptoms.—The symptoms of myoma uteri include: (1) hemorrhage, (2) anemia, (3) pain, (4) leukorrhea, (5) pressure symptoms (constipation, polliakiuria, dysuria, retention of urine). Often there is (6) sterility, or (7) early miscarriages may occur.

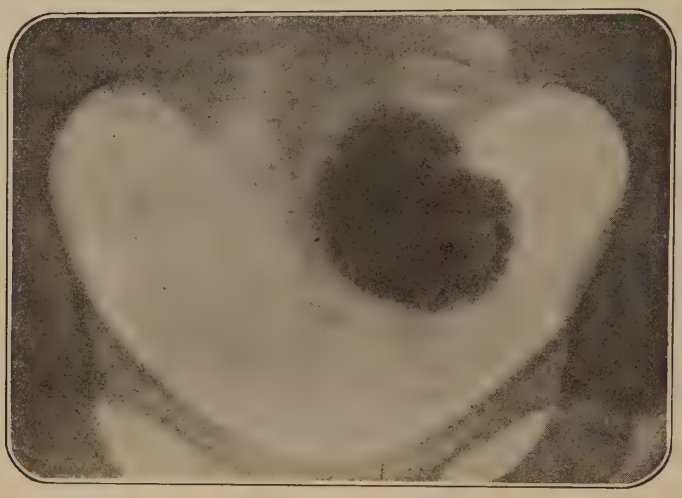

Fig. 494.—X-ray of a Calcifying Fibroid. Note the Uneven Density of the Shadow Cast by the Calcified Mass. (After S. G. Scott, Arch. of the Röntgen Ray, published by Rebman Co., London.)

Diagnosis.—(1) By bimanual palpation, (2) by examination with the uterine sound; or, (3) if a part of the tumor be calcified, by röntgenogram.

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3. Diseases of the Uterine Tubes

(*a*) *Inflammation of the Uterine Tubes* (*Salpingitis*)

Salpingitis may be due to any one of several different causes. By far the most frequent form is gonorrheal infection, which may lead to the formation of *"pus-tubes"* or *pyosalpinx*, more often still to perisalpingeal adhesions (*pelvic inflammatory disease*). Sometimes there is an accumulation of a serous effusion in the tube (*hydrosalpinx*). Tuberculosis of the uterine tube is not uncommon; should caseation occur and the orifice of the tube be occluded, the caseous and purulent material may give rise to a *tuberculous pyosalpinx*.

4. Diseases of the Ovarium

(*a*) *Inflammation of the Ovary* (*Oophoritis*)

An *acute purulent oophoritis* is usually due to infection propagated from the neighborhood, for example from an appendicitis. Hematogenous infections of the ovary rarely occur. *Tuberculosis of the ovary* is usually secondary to tuberculosis of the peritoneum or of the uterine tube.

(*b*) *Tumors of the Ovary*

These include 1. *ordinary ovarian cyst*, 2. glandular multilocular cystoma, 3. *papillary* or *unilocular cystoma*, 4. *cystic carcinoma*, 5. *solid carcinoma*, 6. *teratoma* and *dermoid cyst*, 7. *fibroma*, etc.

For the diagnosis of ovarian diseases, special texts on gynecology should be consulted.

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5. Diseases of the Breast

(*a*) *Inflammations of the Breast* (*Mastitis*)

Occurrence.—Mastitis may be *acute* or *chronic*. It may be *traumatic, pyogenic, tuberculous* or *luetic* in origin. A mastitis may be taken for carcinoma, and *vice versa*.

i. Acute Mastitis

Painful hardening of the breast develops, with fever; sometimes with a chill. The breast often suppurates (*mammary abscess*); in which

event softening in the infiltrated area and fluctuation appear. An abscess may be upon, in, or behind the breast (subcutaneous, parenchymatous, retromammary). Acute mastitis is most common in the early puerperium. Mild mastitis may follow automobile riding, if the breasts are not well protected (colloquially known as "weed").

ii. Chronic Mastitis

Usually tuberculous in origin, it may occasionally be luetic, actinomycotic or rarely, pyogenic. When it develops as an isolated nodule, it may be mistaken for cancer; but tuberculosis in other parts of the body, and enlarged and softened axillary glands, adherent to the skin, speak for tuberculosis. When multiple foci are present, the diagnosis is easier. Histological examination is decisive.

iii. Chronic Cystic Mastitis

The so-called *mastitis chronica cystica* (Reclus' or König's disease) is a degenerative, rather than an inflammatory disease. Multiple nodules appear in *both* breasts, varying in size from that of a pea to that of a cherry or larger. They are common in women over forty and occasionally they are seen in earlier life. They often give the patients great concern lest cancer is developing. The regional lymph glands are often slightly enlarged.

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(*b*) *Tumors of the Breast*

These may be *multiple* or *single*. When *multiple tumors* are present, and especially if they be bilateral, the masses are usually *benign* (cysts; fibro-adenomata). *Caution!* One of these may, at any time, undergo malignant change.

If a *single tumor* be present, it may be (1) small or medium-sized, or (2) larger than a fist.

When *smaller than a fist,* it is probably benign, if freely movable as regards the rest of the breast tissue, malignant if not (even if not adherent to the skin or the pectoral fascia and the nipple not retracted). A cyst may be temporarily immovable and resemble carcinoma, but to the flat hand applied to the thorax a cyst feels indistinct, a carcinoma more distinct; instances in which the movability is doubtful, usually turn out, on operation, to be carcinoma. The patient's own ideas regarding benignancy or malignancy should be wholly disregarded.

Among the *benign growth* are (1) cysts and (2) fibroadenomata. Among the *malignant growths* are (1) carcinomata and (2) sarcomata.

i. Carcinoma of the Breast

A *carcinoma* is not movable as regards the rest of the breast tissue, or only slightly so; this criterion permits of the diagnosis of malignancy before the other, ordinary, criteria (retraction and high position of nipple, enlargement of axillary glands, attachment to the skin and to the pectoral muscles) are positive.

For prognosis, the existence, or non-existence, of metastases is most important. In pains in the back of elderly women, in unexplained sciatica, or in intercostal neuralgia, we should keep metastases in the bones in mind (x-ray), and examine the breasts! Once a breast cancer has become adherent to a rib, or scattered nodules are present in the adjacent skin, or the supraclavicular glands are involved, even extensive operation will probably be followed by recurrence. *Medullary cancers* are soft and grow rapidly; *scirrhous cancer* is hard, infiltrative, growing slowly. A form of flat ulcerous cancer arising from the mouths of the lactiferous ducts and extending through the epithelium to the nipple and areola is known as *Paget's disease of the nipple.*

ii. Sarcoma of the Breast

A *sarcoma,* if infiltrating, can be distinguished from carcinoma only by histological examination. An encapsulated sarcoma, smaller than one's fist, grows more rapidly than a fibro-adenoma.

When a single tumor is *larger than one's fist* it may be (1) a *primary sarcoma* of the breast, (2) a *fibro-adenoma* or *cystadenoma,* or (3) a *cystosarcoma phyllodes.* A tumor that has existed for several years, increasing fairly steadily in size, is probably a *fibro-adenoma;* a sudden rapid growth in a tumor long quiescent indicates *sarcomatous degeneration;* while a tumor reaching a large size in a short time after its first appearance is probably a *primary sarcoma.*

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